ANNALS OF
INTERNAL MEDICINE

VOLUME 12 FEBRUARY, 1939 NUMBER 8

PROPHYLAXIS IN ALLERGY *

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WHEN an allergist, confronted with the difficult and at times hopeless problem of the patient with advanced allergic disease, traces back the story to its beginnings—the severe and perennial asthma, that a few years ago was only an occasional attack, and before that, mild nasal symptoms, untreated because they seemed so insignificant—he cannot help but think how much easier it would have been to help this patient in those earlier stages, and why was nothing done to prevent the onset and progress of his various sensitivities? Although our knowledge of the development of the allergic state is as yet defective and fragmentary, nevertheless enough information is at hand to warrant its practical application. And so some allergists in their writings (Cooke,[1] Rowe,[2] Tuft,[3] Vaughan,[4] and others) have mentioned and most allergists in their clinical practice have advised measures which they felt might prevent the onset of allergic disease. Unfortunately the possibility of prophylaxis has not been brought with sufficient insistence to the attention of internists, pediatricians, general practitioners, and others not primarily interested in allergy. As a result, prophylaxis has been least attempted in the very persons most in need of it: those not yet afflicted with clinical hypersensitiveness, or only in its milder forms. It therefore seemed worth while to present this subject to non-allergists for their earnest consideration and use.

Correct prophylaxis must be based on a knowledge of underlying causes. Here our ignorance sets major limitations. We do not know *why* people become hypersensitive and so we cannot attack the problem from this fundamental aspect. But as to *how* they become hypersensitive we have accumulated both clinical and experimental data on which to base our attempts at prevention. Let us therefore consider the factors which appear to be involved in *how* persons become allergic.

The outstanding etiologic factor in human hypersensitiveness is *heredity*. There are few diseases in which the hereditary factor is more firmly estab-

* Presented before The American College of Physicians, New York, April 5, 1938.
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lished and there is none which is as common in every-day experience. That which is inherited is not a specific manifestation of allergy, such as asthma, or a sensitivity to a specific substance, for example, ragweed pollen, but the ability to become sensitized to a wide range of things in the environment far more easily than do normal persons.

To trace the hereditary factor in allergic disease is not as simple as it is in most hereditary diseases, and for several reasons: The clinical manifestations of allergy are numerous and varied, and commonly of so mild a degree as to go unrecognized as allergic. The things to which persons become hypersensitive as well as the parts of the body so sensitized are very largely a matter of chance and of the peculiarities of an individual's experiences. Clinical sensitivity in those hereditarily disposed may never occur, because the person did not encounter the proper conditioning circumstances that would bring out his hereditary defect, especially if intercurrent disease or accident killed him before the age at which he would probably have developed allergic symptoms. In taking a family history for possible allergy we must therefore be mindful to inquire about a considerable number of conditions that might be of allergic nature, and especially about the milder forms of allergic disease, such as apparently slight food or drug idiosyncrasies, trifling but persistently recurring skin rashes whenever certain things are eaten or touched, mild or severe headaches suggesting migraine, and excessive sneezing—the normal person is entitled to two or at most three consecutive sneezes: if a patient habitually sneezes six times in a row, he is in all likelihood as clearly allergic as if his presenting symptom were severe asthma. We must be prepared to encounter apparent gaps in the story of heredity, especially when a mild type of allergy has been overlooked. A corollary to the latter thought is that whenever possible the family history should be elicited through a woman member of the family, since men are woefully uninformed on these matters.

Heredity seems to be operative in the following manner. The defect appears to be passed on as a dominant characteristic according to the Mendelian law. Since those with the allergic defect are from a genetic standpoint to be considered as hybrids, it follows that, when both parents are allergic, about 75 per cent of the offspring will have the defect. If only one parent is allergic, about 35 to 40 per cent of the offspring will be potential allergics. An important point in the matter of heredity in allergy is this: the more marked the allergic background of an individual, the more marked will be the allergic defect he can inherit, and consequently the earlier in life (infancy!) will allergic symptoms develop and the more varied will they be in the course of his lifetime. While it is by no means the rule, nevertheless there is a definite tendency to find in a patient with sensitivity to inhaled substances a preponderance of inhalant allergy in the family history, whereas the patient sensitive to things ingested more commonly gives a family history of that type of allergy.[5] But above all, the point to be stressed is that the thing inherited is the capacity easily to be sensitized, a

capacity which the allergic carries from the cradle to the grave and which may and often does color the picture of his medical experiences throughout life.

In connection with heredity one must also consider the possibility of sensitization of the fetus in utero. This might occur either by way of passive transfer of sensitizing antibodies existing in the blood of a sensitive mother across the placental circulation, or by the similar passage into the fetus of unsplit proteins of foods which the mother has eaten. In the former instance the fetus would become sensitized to the same food to which the mother is sensitive, in the latter, to some of the foods which the mother happens to have eaten. In man as in the guinea pig the placenta has a covering only one cell thick, which renders that organ much more permeable to substances circulating in the maternal blood than is the case with the multi-layered placental membrane of most mammals. There is both experimental and clinical evidence to show that sensitization of the fetus in the guinea pig and in man may so occur, and in man this may account for the somewhat more frequent history of heredity of allergy through the mother. How important such intrauterine sensitization is in clinical allergy, we do not know. The evidence at hand tentatively suggests that it is not a major factor and that when present it has to do more with sensitivity to foods than to other substances.

What is known of that which tends to bring about sensitivity in those so disposed by heredity? Clinical experience strongly suggests the following factors:

(1) *The ease of permeability of the involved body surface to the sensitizing substance to which it is exposed.*
(2) *The intensity of such exposure, especially with sharply increased concentrations of the sensitizing substance.*
(3) *The increased vulnerability of the exposed surface incident to infection or trauma involving that surface.*

It would follow, then, that the skin with its dry surface offers a fairly effective barrier to the foreign substance. This is in line with clinical experience, for sensitization takes place much less frequently by way of the skin than by way of the mucosa of the digestive or respiratory tracts. Sensitization through the skin is enhanced by moisture which both dissolves the sensitizing substance and makes the macerated skin more permeable. This may be only the increased moisture of perspiration in summer, that, for example, dissolves enough nickel out of the white gold of eye glasses or wrist watch and so accounts for the usual summer onset of such skin sensitivity to nickel. More commonly there is a more obvious exposure to moisture, as in case of the baker, the skin of whose hands becomes sensitive to the wheat protein of the dough which he kneads, or the surgeon who develops a sensitivity to the antiseptic solutions which he uses. Infections of the skin, notably when there are favorable conditions from the standpoint

of moisture, may play a part. The outstanding example is offered by the fungus infections between the toes and the consequent generalized skin sensitivity, termed dermatophytid by the dermatologists, which may arise especially in those of allergic background. Sensitization by way of the skin commonly does not progress beyond the skin to involve other parts of the body.

The mucosa of the digestive tract with its moist surface, its prolonged intimate contact with ingested substances, and its primary function as an absorbing organ, offers a much easier means of entry for the sensitizing substance. Sensitization by way of the digestive tract is therefore a very common occurrence. While in milder cases the sensitivity may possibly remain localized in more or less restricted portions of the gut tube, such sensitivity can and usually does involve any one or several of the body tissues that are capable of acting as shock organs, and so give rise to the most diverse clinical manifestations of allergy.

There are, however, at least two factors operative with regard to the digestive tract that act in a measure against sensitization by this route: cooking and digestion. Cooking commonly applies sufficient heat to alter the nature of ingested proteins so that they may neither act as sensitizing agents to the non-sensitive nor as shock doses to those already sensitized. This accounts for two well-known clinical facts: the greater frequency of sensitivity to foods eaten in the raw state, and the ability of many patients to eat with impunity a cooked food, that eaten raw would provoke symptoms. Digestion probably also in a measure protects against the absorption of undue amounts of unsplit proteins. It has, however, been well established that in this regard digestion is only a very imperfect protection, for it can be shown that tiny amounts of unaltered proteins are constantly being absorbed from the digestive tract. Nevertheless, this imperfect barrier of digestion may under circumstances be still further impaired and so be responsible for the development of sensitization. If this be true, it would in part account for the higher incidence of food sensitivity in infancy when the adequate presence of gastric free hydrochloric acid and consequent normal peptic digestion has not yet been established, and the renewed incidence of such sensitivity in late middle life when gastric anacidity again becomes more frequent. This latter association is, however, by no means constant.

The mechanical factor, stasis, may at times definitely favor the absorption of incompletely digested food, especially if the stasis be high in the gut tube, in the duodenum. Certainly there would appear to be a more than casual relation between duodenal stasis and migraine due to food allergy. Certainly the correction of duodenal stasis is commonly quite as successful in preventing the migraine as is the avoidance of a specific food.

Whether liver disease, by interfering with a possible protective function of that organ against unsplit protein absorbed in the digestive tract, may be a factor in the development of food allergy, as suggested by Urbach,[6] and others, while theoretically plausible, lacks confirmation.

Most vulnerable is the mucosa of the respiratory tract, with its moist surface on which the foreign substances are dissolved, its lack of any digestive mechanism that could protect it, and its contact with the foreign substances in their native, unaltered state. It is not surprising, therefore, that respiratory tract allergies head the list of human hypersensitivities, and particularly so with regard to their severity. Here again a mechanical factor akin to the stasis in the digestive tract may play a part. Thus a marked nasal septal deflection may offer a surface for impingement and lodging of inhaled allergens, thus to favor sensitization in those so disposed by heredity, and to provoke symptoms in the sensitized.

The intensity of exposure to a potential sensitizing agent is an undoubted factor in the development of sensitivity. For example, hay fever patients commonly give the history that symptoms began in that year in which they moved from the city to the country, or in the year in which they motored in early September from their home in New England to Kansas, or in a year in which pollen counts were found to be unusually high. To be emphasized in these examples is the sharp increase in, as well as the high absolute values of the exposure. The concept must be further broadened to include at times long intermissions without exposure between periods of marked exposure. Thus Cooke [1] has stressed the frequency of sensitization to foods that are eaten intermittently but in large amounts, such as shell fish, strawberries, mushrooms, and honey. Drug allergies commonly become manifest in patients who have been treated intensively for a time, then after an interval without treatment, were again exposed to the drug, this time with resultant symptoms.

Increased vulnerability of the exposed surface incident to infection or trauma involving that surface is probably an important factor in the production of sensitivity. Allergic rhinitis and asthma commonly begin after or in the course of a severe, at times protracted tracheobronchitis, such as whooping cough. The pandemic of influenza was followed by a large crop of asthma cases among the sensitizable: infection had rendered their bronchial mucosa more vulnerable; the contents of the room in which they were ill—feathers, cotton, horse hair, dust—were the things to which they were exposed and to which consequently they became sensitized. Since Schloss [7] in 1912 reported the case of the infant who became sensitive to cow's milk first given during a period of enteritis there has accrued both clinical and experimental evidence that sensitization takes place more easily through an inflamed than through a normal digestive tract mucosa. Fungus infection of the skin as a conditioning factor for sensitization has been referred to.

Mechanical trauma to the exposed surface may be the open sesame for the sensitizing agent. Early in his experience the writer was impressed by the fact that at least 5 per cent of hay fever patients gave the history that their trouble had started when an operation of election had been performed on the upper respiratory tract during the particular pollen season.

In short, if we have the inherited defect of becoming easily sensitized,

then operation of pure chance will determine if, when, in what portions of our bodies and to what substances we become sensitive, and the intensity of the conditioning factors will decide how early or late this will occur.

How may prophylaxis be applied in the light of these data?

About the most important factor, heredity, little or nothing that is practical can be done. One might advise the obviously allergic not to mate with each other, but one could not hope for any enthusiastic compliance with such advice. The suggestion has been offered (Rowe [2]) that if existing allergics in the parents be controlled by treatment that the offspring are less likely to inherit the defect. There is, however, no proof for such a claim and it is not in accord with known laws of genetics.

If, then, we cannot alter an individual's heredity, it follows that every effort must be made to control the factors known to influence the development of specific sensitivities.

These efforts should begin with pregnancy, if one or both parents are of clearly allergic strain. What we hope to avoid during pregnancy is the sensitization of the fetus across the placental circulation to foods in the mother's diet. To be sure, there is no proof that the measures about to be proposed will avoid such intrauterine sensitization. Some might be inclined to consider them little more than prayerful gestures. Yet if one be permitted at all to reason by analogy with other clinical experience in the development of sensitization, then the following advice, first suggested by Ratner,[8] is justified: The mother should avoid eating excessive amounts of any particular food, especially if this food has not been eaten for some time. It would be well that she not eat too freely at any one time of those foods which experience has shown to be good sensitizers: sea foods, nuts, raw berries, chocolate. She should be most careful not to indulge freely the dietetic whims and cravings so common in pregnancy. It would be wise to see that her diet is varied, without too much stress on any single food or group of foods. The fetus must experience what should be its guiding rule in later life: moderation in all things.

Prevention of sensitization to inhalants is not only the most important phase of prophylaxis but perhaps also the most satisfactory in its results, in that we are able to a considerable degree to control our environment.

This control of the environment begins in infancy. The nursery should contain as little as possible in the way of dust producers of organic origin. Infants do not need pillows to sleep on, nor does the crib need to be dressed up with a pillow by day. The mattress had perhaps better be made of a good grade of long-staple cotton (not cotton linters!) rather than hair, since sensitization seems to take place more easily to substances of animal origin. If the mattress is covered with some impervious material such as rubberized sheeting, the amount of possible dust exposure is still further reduced. Avoid soft fuzzy blankets of native wool: use instead old blankets that have been repeatedly washed, and preferably dyed, and even then place them in a bag of cotton sheeting. New sheets should be washed before use.

in order to remove substances employed in sizing. The infant should be alone in its room, but if the room is shared with another child or an adult, the bedding of the second occupant must conform in all details.

The bed room floor should be bare, or with at most a small washable cotton rag rug at the bed side. There should be no stuffed furniture and no unnecessary drapes or hangings. The walls should be painted or covered with a smooth hard-finish wall paper, and never with a rough so-called "oat meal" finish paper or with burlap. Bare plaster walls are undesirable because of the dust to which they may give rise, containing at times glue and other sizing materials. Bare walls made of various wood-pulp compositions are also to be avoided. In such a room all dusting can be done with a damp cloth.

Do not introduce any sensitizing dusts, as by spraying the room with insecticides, especially those containing pyrethrum pollen and so commonly used to kill mosquitoes. On the skin use only plain talc or stearate of zinc, not powders containing orris root or perfumes.

At this point it might be well to say something about the house in which the allergic or potentially allergic persons should live. The first point to stress is that it should be high, dry and not too much in the shade. A damp cellar favors the growth of molds whose spores in the house dust may act as sensitizing agents. The house should be heated by radiant heat, not by circulating hot air, and by a furnace burning gas or oil rather than coal. So-called "air-conditioning" devices, if they are provided with efficient filtering units, cut down dust exposure, especially to dusts from without, such as pollens. But if the air is not well filtered they may bring to a bed room, carefully furnished to avoid trouble, the undesirable dust from other rooms with upholstered furniture and heavy rugs. Old houses are perhaps more likely to suffer from the above defects than newer ones, but this is of course an individual problem.

In childhood new and important factors present themselves. There is, for example, the vexatious problem of animal pets. The child with an allergic heredity is best off without pets, or as Vaughan [4] suggests, may be allowed gold fish or an alligator. Yet some well-meaning relative is constantly making offers of a collie dog or a Persian cat. Such offers should be tactfully but firmly declined, at least until the time when the child is old enough not to lavish caresses on the dog or even take him to bed with him. A short-haired dog should then have the preference. It should never be permitted to enter the bed room or to lie on chairs or divans. Flea powders, especially those containing pyrethrum, are to be avoided. Best of all, no pets inside the house!

Almost as bad as live pets are woolly fuzzy stuffed toys. They are commonly made of animal hair and involve unusually intimate and prolonged contact.

As the child grows up, the precautions with regard to the bed room furnishings should not be relaxed. Cotton or kapok pillows, renewed from

time to time as their contents become old and pulverized, are to be used instead of feathers. Plain bed springs are better than box springs, the latter being just one more dust producer and the possible means of bringing in an undesirable unknown filler. There should be no compromise with the bare floor of the nursery. Yet only too often, esthetic considerations win the upper hand and deep-pyle woolen rugs and carpets cover the bed room floor. Even worse than the rugs are the felt pads placed beneath them, made as they are of loosely matted hair of various animals.

In adult years the complexity of our problem obviously increases with the endless variety of possible dust exposures in everyday life. It therefore becomes necessary in large measure to consider the problem from the point of view of the individual. Nevertheless, there are a number of considerations that have a general application.

An important one is the *choice of an occupation.* Those who are sensitizable should avoid occupations that would expose them to considerable amounts of organic dusts. Yet patients are constantly making unwise selections, as did a patient of mine with allergic rhinitis who took up chicken farming and got a feather sensitization and asthma for his pains. Then there are those whose first evidence of allergy developed in the course of their work and for whom it was economically not feasible to change to other work. Black [9] reported the interesting case of a beauty parlor worker who became sensitive to the orris root used by her in a dry-shampoo preparation: by shifting to a buckwheat powder she got relief for a time, only to become sensitized to buckwheat. The same thing happened after she used a rye powder. When last seen she was still symptom-free while using barley flour. Sensitization of workers to organic dusts is receiving increasing attention as an industrial hazard. Thus in one large chemical plant in which some of the workers developed a skin sensitivity to phthalic anhydride, a chemical used in the manufacture of paints, it was found possible to reduce materially the number of workers becoming sensitized by suitable dust control measures.

Members of allergic families should choose their cosmetics with the possibility of sensitization in mind. Especially those containing orris root are to be avoided. Fortunately there is now available an extensive selection of such materials of known composition and made by reliable manufacturers. The less and the fewer the allergic uses in the way of all cosmetics, the better.

Sensitization to pollens may possibly be prevented by avoiding unnecessary excessive exposure to pollens. The sensitizable child should not play in a hay mow. The time and place of a proposed vacation should be selected with a view to possible pollen exposure. Long motor trips inland should not be undertaken at the height of the grass or ragweed seasons in June or late summer, and at these times vacations at the sea shore or the north woods are preferable to those in the country. Those of allergic strain should not live in neighborhoods in which there are large numbers of trees whose pollens are common causes of hay fever: sycamore, paper mulberry, poplar,

birch, oak. Especially to those persons who have already developed one form of pollinosis should these precautions be emphasized, lest they develop an additional type of pollen sensitivity. In fact, it is a common clinical experience when we test a patient suffering, for example, from ragweed hay fever, that he also gives a positive skin test for grass pollen, although he has had no symptoms in June. Such an individual is a potential grass hay fever candidate and should be particularly careful to guard against overexposure to grass pollen. There is ample clinical proof that disregard of this advice is followed by trouble.

Obvious nasal defects of the type mentioned above should be corrected as soon as the adolescent has reached an age at which an operation will no longer adversely affect facial contour in subsequent growth. But the operation should never be performed during a pollen season.

When the potential allergic travels, he will find it advantageous, and not unduly burdensome, to carry with him a cover of rubberized cloth or oiled silk to be placed on the pillow in train, hotel or guest room.

Since inhalant sensitivities would appear to arise more readily when the respiratory mucosa is rendered more vulnerable by an existing respiratory infection, all the measures to guard against sensitization should be observed with meticulous care at that time.

Prevention of sensitization to things ingested is on a more speculative basis than in the case of things inhaled. Yet here, too, there is reason to believe that something can be accomplished.

There is evidence to show that in infants there may occasionally arise a sensitization to foods eaten by the mother and excreted in her milk (Shannon [10] and O'Keefe [11]). It may therefore be suggested that mothers continue during lactation the precautions, mentioned earlier in this paper, to be observed with regard to their diet during pregnancy.

The common pediatric practice of boiling cow's milk before feeding it to infants should be a routine procedure, according to Pounders,[12] for a time with all potentially allergic infants when they are first given cow's milk. The thought is that the boiling will to some degree lessen the sensitizing capacity of the milk.

When the infant is weaned, one must keep in mind the need to avoid overeating at spasmodic intervals of certain foods. One should strive to obtain an early broad diversification of the diet. In so doing, however, one should be somewhat cautious in running counter to the violent dislikes for particular foods which the child so often expresses. One must try by tactful experiment to differentiate between the natural hesitation of most children as well as many adults to try some food never previously eaten (think of the man who ate the first snail or grasshopper) and the violent aversion that at times is an unconscious defense mechanism against a food to which the child is already sensitive. New food, when first introduced into the diet, ought to be fed in the cooked state whenever possible.

Although early diversification of the diet is desirable, it should not be

achieved by giving the young child foods that had better be withheld until later. It would be an obvious folly to give lobster, shrimp, crab or other shell fish too early, and when they are finally permitted, the youngster should not be allowed to overeat, or as the layman so well puts it, " to eat himself sick " of them. Exactly the same precautions apply to nuts and raw berries. Chocolate, a good sensitizer, should be used with discretion. Raw foods, especially raw fruits, and not excluding orange, should be used with discretion, avoiding too much daily repetition or too large quantities of the same food.

These precautions with regard to the diet in childhood should become the habits of adolescent and adult years. Particularly must the subject learn not to overindulge in those foods the intermittent supply of which is dependent on the seasons.

There are medical aspects to the possibility of preventing sensitivity to foods. In the presence of an acute digestive tract ailment, especially in the young, one should be careful not to feed too freely until the digestive upset is over. Perhaps the same caution might be wise to observe for a few weeks when the stomach or intestine has been subjected to an operative procedure. There is, however, no record of sensitization having been observed to develop postoperatively. There is also danger of precipitating sensitization if one too enthusiastically overfeeds the thin in attempting to fatten them. At the same time the physician must remember that if a diet contains too few foods, these will therefore be too often eaten and so might lead to sensitization. Yet this is just what happens to many patients who on doctor's advice or in seeking relief from digestive troubles, avoid one food after another until the dietary has become dangerously restricted. The allergist himself is only too often guilty of this mistake.

Existing functional defects which might lead to sensitization in the digestive tract should be treated or corrected. Commonest is gastric anacidity. But hydrochloric acid therapy must be based on the finding of anacidity by test meal, not on the hunch of the prescriber. Stasis in stomach, duodenum or colon should be dealt with according to the usual indications.

Prevention of sensitization to contact substances in a measure proceeds along the lines already indicated. Moreover there is a good deal of overlapping in the matter of contact, ingestion and inhalation. The infant touches many of the things, the dust from which it also inhales. Mustard may be applied to the skin. as well as eaten. In addition to the advice already given in regard to prevention of sensitization to inhalants in infancy. consideration should be given to the things that might come into long and close contact with the skin, such as dusting powders (no orris root or lycopodium), materials of which clothing are made (silk and wool are more likely to sensitize than rayon, cotton or linen), soaps, oils and creams used on the skin (their composition should at least be known, and their effects noted). Care should be taken to avoid cheap dyes in fabrics or leather, for water-soluble or poorly fixed dyes commonly are causes of trouble.

The number and variety of contacts with substances that can lead to skin sensitization rapidly increase as the child grows. By the time adult years are reached, the problem is even more complex than in the case of inhalants. It must be approached, therefore, in the light of each individual's actual or contemplated environment.

Again, the choice of an occupation looms large, that he may avoid sensitizing contacts. But only too often advice is hard to give in this regard. Careful inquiry into the contact possibilities of a given occupation may apparently disclose no obvious sensitizers, only to be confounded by a report in the next issue of a medical journal with instances of sensitization to things hitherto believed harmless. Moreover, most industrial processes are in a constant state of change, making use of new chemicals and materials, and so introducing new and unforeseen hazards. Yet even so one may apply to advantage the principle that the dry skin is less easily sensitized than the moist.

Cosmetics, by reason of their prolonged and close contact, give rise to a great deal of skin sensitization. The variety of the substances involved may be appreciated by a glance at Goodman's text [13] on Cosmetic Dermatology, the first 188 pages of which are simply a dictionary of ingredients. Those who are sensitizable should therefore be exceedingly cautious in the freedom with which they use such things. As noted above, the less and the fewer cosmetics they use, the better. The same advice applies also to those who live in close contact with the potential allergic: a husband, wife, or room mate. Thus it is a common observation that a man becomes sensitive to the orris root of the face powder used by his wife, and recently one of my patients developed a contact skin sensitivity to the mustache wax used by her husband.

Since hair dyes are capable of producing marked sensitivity, they should be avoided. In fact, some boards of health require of beauty parlors that dye sensitivity be ruled out by a patch test with the dye 24 hours before the dye may be used on the head of a client. Also various dyes, especially inferior dyes, used in fabrics, in furs, and in leather articles including shoes, can sensitize the skin and so should be avoided or at least viewed with suspicion.

The possibility of *prevention of sensitization to drugs* deserves special consideration by us as physicians, for not only are we responsible for the contact with, and ingestion and inhalation of various therapeutic agents by our patients, but often enough we must needs inject into them substances which can and at times do sensitize them.

In infancy it appears to be easier to sensitize skin and mucosa than in later years. Particular thought should therefore be given to the possible sensitizing effect of preparations which we use on the infant's skin or place in its conjunctiva, nose or mouth. At all ages, if a choice is available between an inorganic and an organic drug, the former might well be selected because of the lesser likelihood of sensitization to the inorganic material.

If a drug has once been used freely and then after an interval has to be used again, its renewed application should be watched with care if that interval is over two or three weeks and less than a year, time enough for sensitization to have developed and not enough for sensitization to have worn off.

In treating the potential allergic, one should bear in mind (*a*) those drugs which experience has shown are common excitors of sensitization: aspirin, quinine, ipecac; (*b*) those drugs which give rise to serious types of allergy: malignant neutropenia from amidopyrine, and a number of other substances containing the benzine ring, such as phenacetin, acetanilid, and the arsphenamines; (*c*) those drugs whose long and habitual use, or whose recurrent use in chronic or recurrent disease could induce sensitization, such as phenolphthalein among the laxatives or cinchophen in the treatment of chronic joint troubles.

We should never use horse serum or any other foreign serum as a means of non-specific protein shock therapy, lest by so doing, we sensitize the patient to the serum and so unfit him to receive a specific immune horse serum such as diphtheria or tetanus antitoxin or antipneumococcus serum, were the need for such a serum to arise. Nor should specific serum therapy be undertaken unless the indications for its use are clear-cut and definite.

It is interesting to note that the diabetics who become sensitive to insulin and the patients with pernicious anemia who become sensitive to liver extract are usually found to be of allergic strain. There is nothing we can do to prevent their becoming sensitive, and of course we do not deny them their insulin or liver therapy merely because of the possibility of producing sensitization in them. They do, however, serve as eloquent examples of the possibility of inducing sensitivity by therapeutic procedure.

If the physician himself or the dentist, pharmacist or nurse is the potential allergic, then he should use all possible precautions to guard against sensitizing himself as he handles various drugs. This may mean the wearing of gloves to avoid direct contact when he handles these materials, or even the use of a mask to prevent the inhalation of finely powdered substances.

Avoidance of Sensitization by passive transfer deserves mention. Ramirez [14] reported the case of a man who because of acute anemia from hemorrhage was given a blood transfusion. Some weeks later the patient had his first attack of asthma on coming in contact with a horse. Investigation of the donor now showed that he was himself an asthmatic sensitive to horse dander. The recipient of the transfusion had been passively sensitized to horse dander by the circulating antibodies for horse dander in the blood of the donor. Therefore, since passive transfer of sensitivity by transfusion is possible, and since an appreciable number of individuals are allergic and therefore might have circulating antibodies in the blood, it would be wise to exclude from a blood donor's list anyone with asthma, hay fever or other obviously allergic disease.

To whom shall the attempts at prophylaxis against hypersensitiveness be applied?

1. *The Children of an Allergic Parent.* Especially if both parents are hypersensitive, are we justified in making every effort to prevent the development of sensitivity, since the chances are three out of four that such children will be allergic. Furthermore, the earlier in life such efforts begin the better, for the more marked the heredity factor the earlier in life on the average do these children become hypersensitive. Prophylactic advice should be given, however, whenever we see an individual with this heredity, whether he be child or adult. Thus, for example, it should be routine procedure not only in taking a medical history but in the course of so-called health examinations to inquire about allergic disease in the family history.

2. *Those Who Have Had an Allergic Disease in the Past.* The individual who has had a protracted infantile eczema, or who gives a story of a specific food idiosyncrasy or frequent attacks of hives in childhood, or hay fever in adolescence, is obviously allergic and therefore capable of developing new sensitivities.

3. *Those Who now Have Some Minor Manifestation of Allergy.* In this group the chief point of practical importance to be emphasized is this: We must recognize these manifestations as being allergic: for example, the habitual 10 or 12 consecutive sneezes, the itchy mouth whenever the patient eats certain things, the mild but definite skin rash, the indigestion, the abdominal discomfort, the diarrhea or the headache that always follows the use of a specific food, and many others with which the clinician should familiarize himself by reading an adequate text on clinical allergy.

4. *Those with Obviously Allergic Disease.* It might seem unnecessary to mention this group, whose need for prophylaxis is so self-evident. Yet it is well to remind the reader that these patients, in addition to their major allergic complaint, often have minor forms of hypersensitiveness which they fail to mention, not realizing their true significance. Thus the patient who comes to have his migraine investigated from the standpoint of possible allergy does not tell of his dozen sneezes every morning. Yet they are probably due to an allergic rhinitis that, if unrecognized and untreated, can go on to a serious asthma. Such a patient must not be tested with foods alone, on the assumption that his headaches, if allergic, are most probably due to foods. He should be tested with the usual inhalants and pollens as well. Such routine testing with a wide range of substances will often turn up skin sensitivities not yet associated with clinical symptoms, but which might under certain circumstances lead to clinical sensitivity. The testing of patients with fall hay fever by means of grass pollens as well, as mentioned earlier in this paper, is a variation of this same theme.

How common are the individuals in whom prophylaxis against sensitization might be applicable? It is a conservative statement to say that 15 per cent of the white population of this country is definitely allergic. At least another 10 per cent would be found, on detailed questioning, to have a minor manifestation of hypersensitiveness. The physician in his everyday practice will therefore have plenty of opportunities to put these suggestions to the test.

One might ask: Are not all human beings to some degree sensitizable? The answer is, that experimentally apparently all human beings can be sensitized. But in the great majority of instances it is hard to do so and, as far as clinical experience goes, they do not become sensitized in every day life. The 25 per cent minority, however, with their hereditary defect, are more or less easily and often sensitized, in sharp contrast to their more fortunate brethren.

Summary and Conclusions

1. Since the underlying cause of human hypersensitiveness is unknown, no prophylaxis based on a fundamental etiology is as yet possible.

2. It is clear, however, that the victims of allergy have the characteristic of becoming sensitized to things in their environment far more easily than do normal individuals; a characteristic, in the transmission of which, heredity plays a major part.

3. Increasing clinical experience has given an insight into some of the mechanisms and conditions, by and under which the sensitization to various substances may arise.

4. In the light of such experience it seems not unreasonable to attempt, by applying the information at hand, to prevent the development of sensitivity in those predisposed thereto by heredity, and of new sensitivities in those obviously allergic.

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CHRONIC BRUCELLOSIS (UNDULANT FEVER); AN ANALYTICAL STUDY OF THE POSITIVE REACTORS AMONG SCHOOL CHILDREN *

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THE United States Department of Agriculture in the past few years has made an extensive survey of the incidence of Bang's disease among dairy cattle in the United States. It was found that an average of 38.4 per cent of the herds tested contained positive reactors. In the infected herds 14.9 per cent were positive, of the total 11,858,859 cattle 8 per cent gave a positive agglutination test.[1]

Although there were reported in the United States a few scattered cases of undulant fever as early as 1904 its clinical recognition as a common infection dates from 1926. Our present knowledge of Brucella infection may be divided into three phases: first, the general recognition of the acute variety of the disease; second, the recognition of various complications; third, investigation of the ambulatory, subclinical and latent infections which have been classified by many observers as cases of chronic brucellosis. It occurred to us that if there is serological evidence of such wide infection in dairy cattle there should be more evidence of infection in human beings.

Therefore, we outlined a plan of study in the city of Kansas City, Kansas, for skin testing grade and high school children. While members of the State Board of Health were testing with tuberculin we applied intradermal brucellergin tests on the opposite arm. We chose children for study because they are the largest milk consumers, although the acute variety of the disease has been infrequently reported in this group. In collaboration with Baumgartner [2] and Lunsford 7,122 children were so tested. Divided into age groups, there were 5,809 from 10 to 19 years and 1,213 from 4 to 10. A positive allergic skin test was obtained in 642 or 9 per cent. Impressed by this rather surprising information we decided to question parents of the positive reactors about the occurrence of chronic complaints in their children. Nurses from the Health Department of the city were directed to complete a questionnaire as shown in figure 1. The nurses were carefully instructed not to ask leading questions but to ascertain as nearly as possible the present physical condition of the child. We excluded from this study 132 children who gave a simultaneous positive tuberculin test. The first questionnaire was completed in April and May of 1937. A follow-up survey was made in February 1938, in which the parents of 374 positive reactors were recontacted.

* Delivered before the American College of Physicians, New York City, April 6, 1938.
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We wish to acknowledge the coöperation of Dr. W. F. Lunsford, Director of Health, Kansas City, Kansas, and Drs. Leona Baumgartner and Alice Evans, National Institute of Health. Without their assistance the collection of this material would have been impossible.

FIGURE I

THIS HISTORY FOR THE PAST TWO YEARS

Name ..... Address .....
Age ..... Sex ..... School Grade ..... No. of other children in family .....
Does child drink—Raw ..... Pasteurized ..... Canned milk .....
Contact with cows (milking etc.) ..... Name of dairy .....
Weight chart .....
School record—Bright ..... Dull ..... Medium ..... Attendance .....
Chronic ailments .....
Constipation ..... Temperature ..... Headache .....
Night sweats ..... Rheumatism ..... Neuritis .....
Peculiar pain or aches .....
Nervous symptoms: Depression .....
Irritability .....
Tuberculin test .....
Are there any other members of the family ill? .....
Possible diagnosis .....
Has diagnosis and treatment of undulant fever been made? .....
Condition of mouth and teeth .....
Family physician .....

Our questionnaire was devised with the symptoms enumerated because we have encountered them frequently in chronic brucellosis. Some other symptoms frequently met with as excessive fatigue, lassitude, weakness and anorexia were omitted because of their indefinite character. The complaints recorded were chronic in nature and not those which accompanied acute or transient illnesses. When the symptoms were tabulated we combined similar symptoms into groups to eliminate duplication and to prevent undue emphasis on a single symptom as shown in table 1. Rheumatism,

TABLE I

462 Reactors Studied

Nervous symptoms	208	44.3%
Headache	172	37.2%
Rheumatic symptoms	157	34.0%
Constipation	71	15.3%
Fever	22	4.8%

neuritis, aches and pains were put in a group of rheumatic symptoms. Constipation was not classified as a symptom unless it occurred concomitantly with other symptoms. The largest group was the nervous symptoms in which depression, irritability, emotional instability and other psychomotor phenomena were noted. This coincides with the frequency with which these symptoms occur in known cases of chronic brucellosis. The order of the other symptoms in frequency was headache, rheumatic complaints, constipation and fever.

Tabulations were made of the symptoms present by the first questionnaire in both the total number studied and in those who were followed. These are shown in table 2. In order to determine those in whom the symptoms were most likely to be significant of chronic illness we eliminated those who had less than two symptoms by the classification in table 1. Accordingly, of the 462 studied in 1937, 179 or 38.7 per cent had two or more

TABLE II

Number Symptoms	1937 Total	1938 Follow-up
0	116	100
1	167	135
2	80	61
3	47	35
4	32	27
5	20	16
	462	374

First group 462, two or more symptoms in 179 or 38.7%
Second group 374, two or more symptoms in 139 or 37.1%

symptoms while in the group of 374 followed in 1938, 139 or 37.1 per cent had two or more symptoms. The group followed then can be said to be comparable though the total is less.

From the follow-up study it was found that in 80 of the 139, symptoms persisted to some degree as shown in table 3. This represented 57.5 per

TABLE III

1938 Follow-up

Reactors with 2 or more symptoms	139
Symptoms persisted in	80
Per cent	57.5

cent of the reactors who had two or more symptoms and is a further indication of the chronicity of the complaints. Some reported additional complaints as fatigue, lassitude and anorexia. In spite of this, the majority were reported to be making satisfactory progress and gaining weight.

One hundred students of the same age group were chosen as a control. These students had negative tuberculin and negative brucellergin tests. The results of this study are shown in tables 4 and 5.

TABLE IV

100 Control Students

Nervous symptoms	26	26%
Headache	15	15%
Rheumatic symptoms	6	6%
Constipation	2	2%
Fever	1	1%

TABLE V

100 Control Students

Number Symptoms	
0	67
1	20
2	10
3	3

Two or more symptoms 13 or 13%

It is apparent that there is a higher percentage (38.7 per cent) of the children with two or more symptoms in the group under investigation than

in the control group (13 per cent). It was interesting to note that many so-called normal children had chronic complaints.

Comment. As the result of this study it was thought advisable to secure the opinion of professors of immunology and bacteriology concerning the specificity of antibodies.

Twenty-six replies were obtained from a questionnaire asking their opinion concerning agglutinins, opsonins and allergic skin reactions for Brucella infection. A tabulation of their response is shown in table 6. It

TABLE VI

Specificity of Antibodies
26 professors

	Yes	No	Don't Know
Agglutinins	17	1	8
Per cent	65.4	3.8	30.8
Opsonins	8	3	15
Per cent	30.8	11.5	57.7
Allergic Skin	10	1	15
Per cent	38.5	3.8	57.7

was apparent that those who have had experience with Brucella infection believe that these clinical diagnostic procedures indicated past or present infection. We wish to make it clear that evidence of infection does not mean disease. Individuals may give positive serological or allergic evidence of Brucella infection with or without clinical symptoms. The diagnosis of acute or chronic brucellosis, as does the diagnosis of tuberculosis, rests upon clinical symptoms and signs plus certain immunological or bacteriological evidence. There is no group of symptoms which are characteristic of chronic brucellosis, in fact, the variety and vagueness of the complaints are features of the disease. While the symptoms encountered in the group studied may have resulted from other obscure infections or unrelated conditions, the fact that they occurred so frequently in the students with positive skin reactions warrants more than casual consideration.

Neurological complaints were found in 44.3 per cent of the reactors. This is of particular significance in view of the fact that in chronic brucellosis these complaints usually predominate.

It is not our purpose in this study to show that all of these positive reactors are actually suffering from chronic brucellosis of the ambulatory type. We are only reporting that a large number of children in the two surveys completed are suffering from chronic complaints which may be the result of Brucella infection. Careful clinical analysis of each individual case would be necessary to prove the above assumption. The consent of the parent and the family physician would be required to accomplish this. After consideration, we decided this would be impractical in our community.

Adequate cultural methods for the isolation of the Brucella are not now available. Among others, the National Institute of Health, under the direction of Dr. Alice Evans, is conducting research in this direction. When more practical laboratory procedures are devised for isolation the diagnosis of chronic brucellosis will no longer rest almost wholly upon clinical and immunological criteria. This appears to be our greatest handicap in the study of the chronic phase of the disease.

In the private practice of medicine we are too frequently confronted with patients who have definite subjective symptoms and in whom we are unable to make an adequate diagnosis. We believe with more careful clinical investigation and laboratory studies that many patients in the group referred to above could be classified as victims of chronic brucellosis. This applies not only to children but to adults.

Conclusions

1. Evidence of chronic illness was found in 179 children or 38.7 per cent of 462 positive brucellergin, negative tuberculin reactors studied in 1937.
2. Persistence of symptoms was noted in 57.5 per cent in 1938.
3. Control studies indicated that there was a higher percentage of children with chronic illness in the group under investigation.
4. Replies received from 26 professors of immunology indicated that the presence of agglutinins, opsonins and allergic skin test are specific reactions for present or past Brucella infection.
5. Immunological evidence of Brucella infection does not mean disease. The diagnosis of chronic brucellosis depends upon clinical findings plus some positive laboratory data.
6. The ambulatory and subclinical types of Brucella infection are apparently not uncommon.

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VARIATION OF BLOOD PRESSURE WITH SKELETAL MUSCLE TENSION AND RELAXATION *

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THE welter of enumerated causes of blood pressure in health and in essential hypertension suggests that perhaps among them we have been neglecting some factor more or less familiar to all, the clear-cut recognition of which might aid us in the long run to understand problems of high blood pressure a little better. Whatever factor we suspect obviously can be better estimated if we can succeed in measuring it simultaneously with the blood pressure.†

Current opinion on the significance of vascular tonus is summarized [1] in a recent review by Fritz Lange.[2] In hypertonia the blood vessels are evidently hyperexcitable. That the arterioles together with the splanchnic arteries are mainly responsible for the regulation of blood pressure is generally conceded today. Functional constriction of these arteries appears to be the probable cause of hypertonia, or of what Hochrein terms a permanent increase in the tonus.[3]

Some 18 years ago clinical observations of hypertensive patients suggested that they characteristically held various skeletal muscles somewhat rigid or over-contracted or that they moved excessively, and in an experimental manner I began to train such patients to be more relaxed. The method seemed applicable to patients characteristically tense, with and without attendant high pressure, and a preliminary reference to some results was included in 1920 in an article entitled, " Use of Relaxation in Hypertensive States." [4]

Clinicians recognize that pressure is likely to be higher in a patient when he first walks into the office than a little later on. They note also that the pressure is likely to be higher upon admission to the hospital or on the first day or two than on subsequent days, particularly if the patient remains persistently in bed. That the blood pressure is lowered in sleep is common knowledge from the observations of Howell and others.[5] Such observations on patients in the clinic or at the bedside are more or less casual and generally are interpreted as variations of pressure due to emotion. Conditions are

* Aided by a grant from the National Research Council.

Aid also is gratefully acknowledged from the Bell Telephone Laboratories, including indebtedness to the late Mr. H. D. Arnold for his kindly interest and to Messrs. H. A. Frederick and D. G. Blattner.

Preliminary or partial reports were read before the Chicago Society of Internal Medicine, Feb. 24, 1936, The American Physiological Society, March 27, 1936, and the National Academy of Sciences, November 18, 1936.

From the Physiological Laboratory of the University of Chicago and the Laboratory for Clinical Physiology, Chicago.

The experiments were conducted with the aid of William M. Lees.

† Hypertension of cardiac and renal origin lie beyond the scope of the present article.

not as a rule controlled and no attempt has been made toward distinguishing the influence of muscular tension from that of emotion.

Pertinent are the following observations made in 1929 on " Bh," whose blood pressure had been frequently recorded ever since December 1918, when he was 38 years old, and who had received a partial training in relaxation by what is called an abridged course. A portion of his earlier medical history has been published previously. He was inclined to be hypochondriac and at one time showed visceroptosis. Attacks of abdominal pain occurring prior to February 1928 and accompanied by the appearance of erythrocytes and leukocytes in the urine seemed due to ureteral spasm. A roentgen-ray examination disclosed a horse-shoe kidney. The figures recorded in table 1 were secured in 1929 with a stethoscope plus the palpatory method of taking blood pressure. Although initial pressure upon lying down is 146 systolic and 86 diastolic there occurs with continued relaxation a progressive fall during the succeeding hour of 26 mm. in systolic and 8 mm. in diastolic pressure.

TABLE I

Blood Pressure During Relaxation in a Subject Lying Down

Position	Time (Min.)	Pressure (Mm. Hg)	Pulse
Sitting		140/84	
Lying	0	146/86	
	7	140/82	112
	37	132/80	96
	54	120/78	84

A common misapprehension is that an individual must lie down if he is to relax. The figures in table 2 are from tests with the same subject on another occasion in 1929 during relaxation in the sitting posture.

TABLE II

Blood Pressure During Relaxation in a Subject Sitting

Position	Time (Min.)	Pressure (Mm. Hg)	Pulse
Sitting 2:00 p.m.	0	154/84	120
	1	154/84	
	2	152/82	
After ½ hour relaxing 2:30 p.m.		128/78	111
		128/78	
		132/79 (after coughing)	
After ½ hour further sitting but not relaxing 3:00 p.m.		138/78	106
		134/78	
		138/78	
After 1 min. clenching left fist (pressure taken on right arm)	1	148/84	111
	2	154/88	
	3	158/82	

These observations following an initial level of 154 systolic and 84 diastolic show a fall of blood pressure amounting to about 26 millimeters systolic and 6 millimeters diastolic after ½ hour of relaxation in a sitting position. After a further period of sitting, with instructions not to attempt to relax, the pressure rises moderately. Clenching the left fist thereafter evidently causes the pressure to rise, so that it returns to approximately the initial level.

In order to evaluate the influence of skeletal muscle tension on blood pressure we shall need to obviate or render minimal the effects of posture as well as of emotion. Another requirement for a systematic study has seemed to be an instrument capable of measuring muscular tonus accurately and in sufficiently slight states. Measuring muscle tension in intact man is no easy problem. It is not sufficient to measure contraction in muscles which are markedly rigid or which are in obvious motion; more than this, we need to be able to detect and to measure contraction in muscles which are apparently quiet; for even here the muscles may or may not be in various states of slight or moderate contraction.

No one has succeeded in overcoming these difficulties through measuring muscle tonus in intact man by mechanical means. The string galvanometer alone is not sensitive enough for the problem on hand. As early as 1922, when surface electrodes of suitable nature were attached to the flexor muscles of my own right arm, no adequate recording was secured at moments when I felt very slight contractions in that locality. Accordingly, I set out to develop or assemble apparatus which would magnify the responses obtained from the string galvanometer. This search was materially aided by the development in the amplifying power and stability of vacuum tubes due to the efforts of various physicists and radio engineers. In 1921, Forbes and Thatcher of Harvard first used an amplifying equipment together with the string galvanometer for the study of electrical changes during muscle action in man.[6] Since that time other investigators have used various types of similar equipment but never, I believed, sufficiently sensitive for the present type of study on muscular contraction. There is no difficulty in constructing apparatus that will give sufficient sensitivity, since adding an extra tube or more always tends to give additional magnification. But with each such addition the instrument itself becomes increasingly unstable. In consequence, the string vibrates so largely and irregularly, even when a short circuit exists across the input terminals of the amplifier, that the instrument is useless in fine measurements. Accordingly the physical problem in developing a suitable instrument centers chiefly around the elimination of sources of electrical disturbance arising both within the instrument itself and in the room or environment in which the instrument is placed. The history of the development of the instrument used in the present studies and of how disturbances were gradually reduced or eliminated has been told elsewhere.[7] It has proved possible to devise and assemble equipment that can be set at one thousand or more times the voltage

sensitivity of the string galvanometer as currently used in taking electrocardiograms, while the base-line shows only one or two millimeters more fluctuation than the base-line in a satisfactory electrocardiogram.

Procedure

Measurements of blood pressure and simultaneously of muscle tension by the action potential method were made in approximately 50 subjects. Approximately 38 showed normal pressure and 12 chronic vascular hypertension. Nine of the former and five of the latter had been previously trained to relax.[8] The subject lies comfortably in a quiet room to favor relaxation and to keep disturbing factors as far as possible constant. For shielding purposes, the couch is enclosed in a grounded metal box, but the cover can be left open and the ventilation is quite satisfactory. In a few experiments, the subject sat in a chair completely enclosed in a grounded copper screening. Electrodes consist of platinum-iridium wires, gage 22, or finer, but with sharpened points so that they penetrate the skin readily. These wires are bare for about half an inch, but are covered in their remaining portion by rubber insulating tape. This tape covers also the junction of the electrodes with the copper wires leading to the amplifier. In all of the records here to be reported, measurements are taken from the flexor muscles of the right arm. One electrode is inserted to the full length of the exposed wire into the arm flexor muscles below the nervous equator of Piper. This is called the "positive" electrode, being connected with the inner winding of the input transformer of the amplifier. The other electrode ("negative") is inserted about two inches below hypodermically in the elbow-pit in the attempt to secure a relatively indifferent location; but this attempt is far from wholly successful. In some instances a second pair of electrodes is inserted into the abdominal wall, about two inches from each other, above or below the umbilicus, but in such a line with the heart axis that a minimum record from the heart action is secured. A third pair is sometimes inserted in the left quadriceps femoris muscles, again two or three inches apart. Sometimes a fourth pair lies in the region of the right eye, one in the middle of the eyebrow and the other hypodermically about half an inch lateral to the external canthus of the right eye.

During early experiments, when two separate pairs of leads were used and I had but one recording instrument, a Cambridge string galvanometer, it was necessary to alternate, for example, taking the record from the right biceps region for a few minutes and then switching to the abdomen. At a later time, after the addition of a Sanborn outfit, two complete amplifier-galvanometer assemblies became available. Thereafter it was possible to take records solely from the biceps region as well as from the abdominal or other region selected during the entire period of experimentation; but in some experiments a changing off arrangement was used with each instrument, making it possible to secure records from four different muscular regions, each for approximately 50 per cent of the time of the study.

The photographic paper was generally run at about two inches per second or thereabouts. For purposes of economy, the shutter in one or both cameras is opened automatically by a relay device three times per minute for periods of about three seconds only. When both cameras are used, the on and off periods are identical for both.

During preparations, which take 15 minutes or more, the subject commonly lies on the couch and is encouraged to have his eyes open and to converse. But when the recording begins, he is instructed not to speak nor to open his eyes thereafter.

The presence of the electrodes in the tissues creates no noteworthy psychic disturbance and may be neglected for the purposes of the present study. There is but slight pain and this as a rule is chiefly from the initial penetration. When I have relaxed under these conditions, it has been evident that no pain continues. Previous to insertion the electrodes are immersed in 95 per cent alcohol for periods of five or ten minutes and the skin is cleansed with the same solution. The electrodes are permitted to dry in the air before insertion. While a greater dilution of the alcohol would have a higher germicidal action, I have preferred the stronger solution because it dries more rapidly. No infection has occurred.

Blood pressure is taken from the left upper arm. To eliminate subjective errors in readings the Tycos self-recording sphygmomanometer is employed as a rule. This instrument, we may assume, accurately records as a rule the systolic blood pressure, with an error which is probably negligible. The literature cited by the makers of this instrument fails to show that the diastolic readings have been sufficiently standardized. In some of the records there has been considerable doubt in my mind concerning the precise reading of diastolic pressure. Under these conditions, I present the readings for what they are worth. In the long run any errors in the recorded diastolic pressure probably do not influence the general character of our results.

With each galvanometer, string tension is set at approximately one centimeter deflection for three or four millivolts, when impressed upon the string terminals directly. From time to time throughout the period it is necessary to adjust the string tension in the Sanborn outfit so as to keep the deflection constant for a particular voltage so impressed. Such readjustments are not required with the Cambridge outfit.

We begin each period of measurement by taking in about two minutes records of the vertical time lines, occurring at intervals of one-fifth second as made with a tuning fork; of the string excursion per millivolt impressed upon its terminals; of the string excursion when one microvolt is impressed upon the input terminals of the amplifier; and of the irregular excursions of the string shadow while the amplifier input leads are short-circuited by means of a switch. Such excursions, expressed in microvolts, are one measure of the error of the instrument and, along with the width of the

string shadow, must be subtracted from the lines or magnitudes recorded during measurements of potential differences in the electrodes.

These features are illustrated in figure 1, *a, b, c, d.* In figure 1 *a* are shown a few seconds of record of action potentials from a muscle when somewhat tense. We measure in mm. the longest (vertical) line in each unit of time, 0.2 sec. From this we subtract the length of the average of the longest lines obtained from short-circuiting of the input leads of the amplifier (figure 1 *c*). The resultant is translated into microvolts (figure 1 *b*). This gives the maximum peak voltage per unit of time, 0.2 second. The average of these maxima is determined for each film exposure of several seconds and three such determinations per minute are plotted as action potentials against blood pressure in subsequent figures in this article. In a muscle completely relaxed, the vertical lines (aside from those due to the heart beats) are no longer than those present upon short circuit (compare figure 1 *d* with figure 1 *c*).

Action potentials are recorded as a rule during periods of 75 minutes or longer. Three blood pressure readings are made both initially and finally with five minute intervals. Every effort is made to be quiet and unobtrusive so as to disturb the patient as little as possible.

Results

Investigation appropriately begins with "normal" subjects not trained to relax lying down under conditions kept favorable for relaxation. The subjects were secured chiefly from the employment office of the University of Chicago. A few were from athletic teams. They ranged in age from 18 to 26 years except that one was 31. All were paid for their time. Records were discarded if the subject gave a history suggestive of hypertension. Another record was excluded on statistical grounds, as a "sport" which would distort the mean value, because the action potentials were far in excess of those of other subjects. A total of 19 records from 17 different subjects is included in the results shown in figure 2.

In this composite graph, the initial drop in pressure characteristic upon reclining does not appear, since, in order to eliminate this, blood pressure is not taken until the subject has been prone for about 15 minutes. During the subsequent interval of uninterrupted 45 minute rest, some of these untrained subjects display practically perfect relaxation often for minutes at a time in the arm flexor muscles, but less often in the abdominal group.* However, on the average, they do not relax completely in the groups tested. Tensions range irregularly up to 2 and a little beyond, measured in microvolts and averaged. Such a state of incomplete relaxation while lying down we term "ordinary rest"; here as well as in foregoing studies, we have found that relaxation is frequently incomplete in subjects not trained to

*Unfortunately, the number of such instances, where relaxation was attained at least in one set of muscles, as well as the number of instances of high tension, was insufficient to enable us to classify and compare the results from the two types.

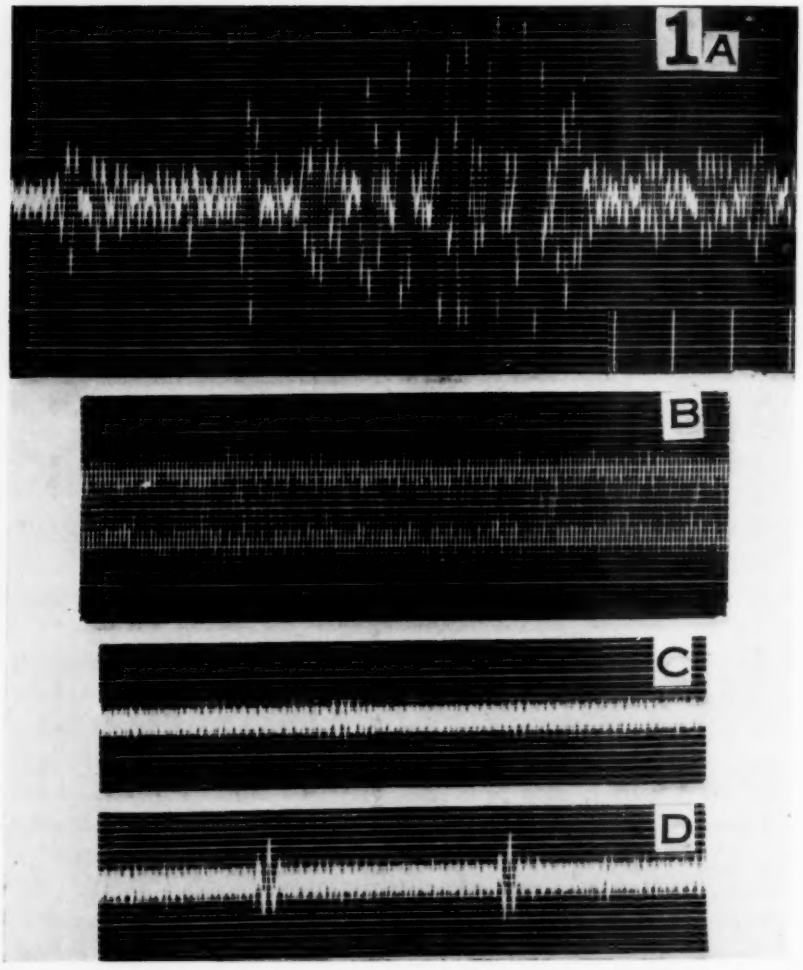

FIG. 1, *a*. Showing marked fluctuation in action-potentials from electrodes inserted into the right arm flexor muscles in a hypertensive patient lying down and attempting to relax. The greater the potentials, the greater the length of the approximately vertical lines. In right lower corner, time-lines denote intervals of 0.2 sec. They apply also to *b*, *c* and *d* of figure 1.

b. Calibration potential, 1 microvolt at 57 cycles per sec. Note that the overall peak excursion is approximately 15 mm.

c. Because of the high sensitivity, the string vibrates slightly, even when the subject is not in line but a short circuiting wire is across the input leads of the amplifier. The peak excursions shown here amount to almost 5 mm. To calculate microvoltage of each vertical line in figure 1, *a* subtract 5 from its length in mm., then divide by 5.

d. Showing approximately perfect relaxation (zero value of action-potentials) from electrodes inserted into the right arm flexor muscles of a patient trained to relax. The two sets of longer double lines (each almost 1 cm. long) represent heart voltages as here recorded. Intervening between these two sets, the record shows vertical lines approximately no longer than those shown in figure 1, *c*.

relax.[7, 9] As evidenced in figure 2, ordinary rest (omitting the first 15 minutes upon change of posture) fails in the present subjects to effect any marked fall of blood pressure during the period.* The current belief that prolonged lying down (regardless of muscle states) continues to reduce pressure is not confirmed.

In this group of 19 records from subjects with " normal " blood pressure, the initial systolic pressure (after about 15 minutes rest) is between 98 and 120 in 12 instances, which is 63.2 per cent; while the diastolic pressure is

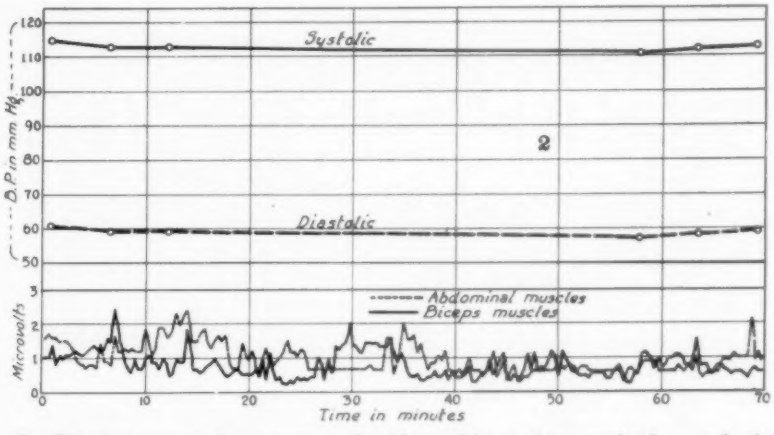

FIG. 2. Blood pressure in seventeen healthy subjects (not trained to relax) during "ordinary rest." The subjects have been lying down for about 15 minutes previously. Averages from 19 records are included, since two subjects are represented by two records. Blood pressure as well as action-potentials from abdominal and right arm-flexor muscles are plotted against time. See text for methods of recording and calculation.

As will be seen, the subjects on the average fail to relax completely, for the microvoltages from both sets of muscles vary irregularly up to two or somewhat more. Under these conditions of moderate relaxation, which we call "ordinary rest," the blood pressure remains practically stationary during the period of seventy minutes.

between 60 and 70 in 13 instances, which is 68.4 per cent. The highest systolic pressure is 134, the lowest 89; while the highest diastolic is 75, the lowest 43. Comparing the fourth pressure reading with the initial one, the change, systolic, ranges from a fall of 11 millimeters to a rise of 7

* It is doubtful that a difference amounting to no more than a few millimeters has any significance in blood pressure studies because the method of taking blood pressure is of limited accuracy and because blood pressure itself fluctuates in many individuals from time to time by at least a few millimeters. We note that the third reading of pressure, ten minutes after the first reading, is two millimeters less, both in systolic and diastolic pressures. Ignoring these doubts, the slight drop mentioned perhaps is a continued after-effect of the previous postural change; or perhaps it is due to the relative diminution of muscle tensions and their reflex or other effects on blood pressure; but other explanations are possible. The sixth (final) blood pressure reading is practically identical with the third. These two readings are made under analogous conditions since in each the subject presumably has been disturbed twice previously by noises of inflation and by the pressure on his arm—factors that might slightly affect the results. For similar reasons, comparing the fifth with the second reading, the values are approximately the same. It is true that the fourth reading, both systolic and diastolic, is 4 mm. below the first. If significant, this slight difference is perhaps explainable as due to the influence of the partial relaxation present during the previous prolonged rest; but the fact remains that two out of three of the readings after the 45 minute rest show practically no fall of pressure.

(excepting one instance of 23 millimeters fall); the change, diastolic, ranges from a fall of 13 to a rise of 9 millimeters.

The results with a patient not trained to relax but complaining of nervousness and restlessness are shown in figure 3. As will be seen, there was marked failure to relax, particularly in the flexor muscles of the right arm. Like the average for the subjects shown in figure 2, her blood pressure fails to fall during the 75 minute period lying down.*

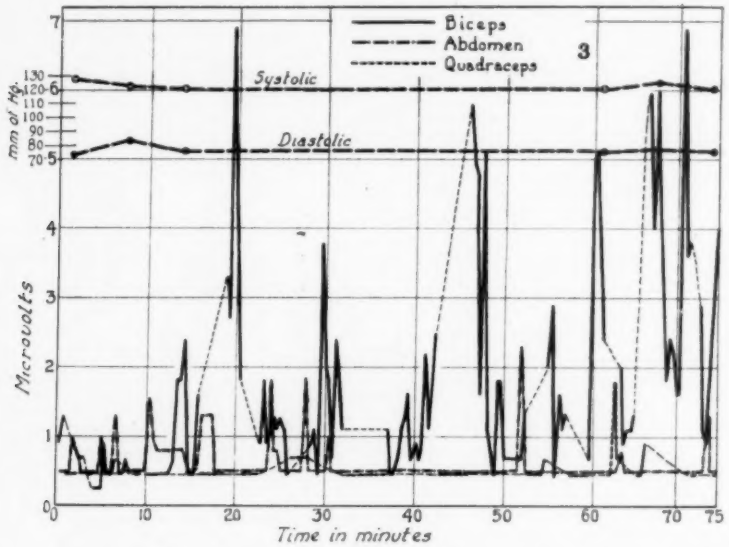

FIG. 3. Record of a nervous patient, showing failure to relax while trying to do so, lying down. Time in minutes begins at 0, when she has already been resting for about 15 minutes previously. In the right arm-flexor muscles, microvoltages vary greatly, at times almost reaching seven. However, the abdominal muscles show less microvoltage, often remaining continuously at about one-half and seldom beyond two. Likewise, the left quadriceps muscles show still less microvoltage, often remaining continuously at about one-half and seldom beyond one. (For the abdominal musculature in this graph, recording is performed continuously with the Cambridge outfit by the sampling method described in the text. However, the recording from the biceps muscles with the Sanborn outfit is interrupted at the times indicated by lighter broken lines connecting the heavier continuous ones. At such times is taken the record for the left quadriceps muscles.)

During this 75 minutes with relaxation incomplete, the blood pressure remains practically stationary.

The influence of relaxation is conveniently studied in patients trained to relax. "Ve," who complained in 1930 of spells of stammering and stuttering and occasionally manifested symptoms evidently due to an irritable colon, had normal blood pressure. Although trained to relax he did not meet with equal degrees of success on all occasions.

* I am grateful to Dr. A. T. Kenyon of the University of Chicago Clinics for referring this patient and for the following notes: She complains also of pains in the head, right flank and elsewhere. Thyroidectomy four years previously, but basal metabolism now + 1 per cent. She dates her present symptoms from pregnancy, fourteen months ago. No organic pathology found, except marked lumbar lordosis. Wassermann and Kahn negative; hemoglobin, 80 per cent, red blood cells, 4,230,000; urine, negative.

In figure 4 are graphed the results for the half-hour period, when the subject appears to lie very quietly, showing no tension grossly manifest to the naked eye. Action potentials from the right arm flexors continue approximately at zero level throughout. It is unusual in my experience for a patient to show such prolonged, uninterrupted relaxation in a muscle group unless trained to relax. Nevertheless the record shows that the abdominal muscles fail to relax completely; at certain moments the peak microvoltage reaches 12. Notwithstanding the advanced degree of relaxation in the arm flexors, the systolic blood pressure ranges from 120 to 114 and the diastolic from 77 to 60, which is about on the same level as when he lies down in

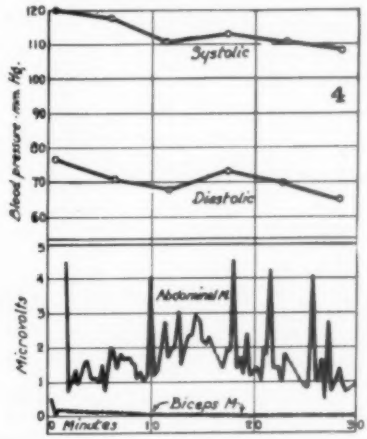

FIG. 4. Partially successful relaxation in a nervous patient previously trained to relax. "Time in minutes" begins at 0, when he has already been lying down for about fifteen minutes previously. Relaxation continues practically complete in the right arm-flexor muscles throughout the record. However, he fails to relax the abdominal musculature, for the microvoltage seldom falls below 1 and often exceeds 4.

Blood pressure readings are made every five minutes, showing a slight fall toward the end of the thirty minute period. The range is from 120/76 to 108/65.

ordinary rest and at times clenches his fist, as shown by another record not here presented.

Upon the occasion represented in figure 5, however, relaxation is evidently more generalized than in figure 4 and there is lower pressure, both systolic and diastolic. After the pressure is once taken, the microvoltage of the right arm flexors continues at approximately zero, while that of the abdominal and of the left quadriceps femoris muscles seldom reaches and never exceeds one. An exception to this statement is the time (approximately at 21 minutes) when he falls asleep and evidently loses conscious control of his muscular states, whereupon the microvoltage of the right arm flexors becomes almost 5. This rise is but momentary, for, upon being awakened, he quickly regains control and relaxes promptly. Throughout the record in figure 5, the systolic pressure ranges from approximately 105 to 100, which is 15 to 14 mm. below the range in figure 4. The consideration

that blood pressure varies somewhat even in the same individual from day to day would not justify us to cast aside these data, if only because we are here engaged in determining some of the factors that evidently are responsible for such fluctuations. On several other occasions when this subject was not so completely relaxed, the pressure was notably higher. A fall is seen also in the diastolic pressure (vide supra), since the range in figure 5 is from 59 to 52 mm. in contrast with 77 to 60, a reduction ranging from about 18 to 8 millimeters.

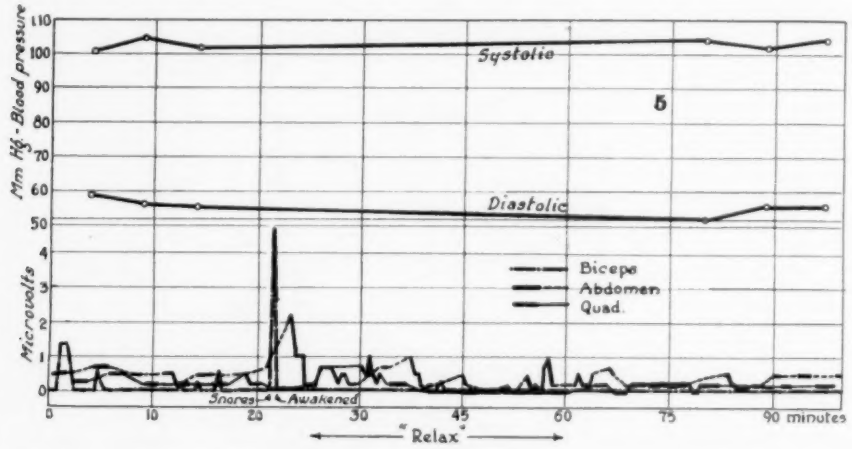

FIG. 5. More successful relaxation in the same patient on another occasion, as compared with figure 4. The right arm-flexor muscles, recorded continuously by the sampling method with the Sanborn outfit, show an absence of action-potentials practically complete, except at one time (about 21 minutes after the beginning of the record, which is about 36 minutes after he lies down). At this time he falls asleep and action-potentials appear, mounting above 4 in microvolts. Upon being awakened, he quickly regains control and relaxes again promptly and completely. Aside from this moment of going to sleep, action-potentials from the abdominal and right quadriceps muscles range at times up to 1 microvolt, but in general at about one-half microvolt or below.

Under these conditions, the blood pressure remains approximately stationary during the ninety minute period of observation, but the range is 105/59 to 102/50. This range is distinctly lower than that in figure 4, at least in so far as the maximum systolic pressure is 15 mm. less than that in figure 4 and the maximum diastolic pressure is 16 mm. less than that in figure 4. While the lowering is less marked in the comparison of minimum pressures, the results indicate a difference which is probably significant and is most likely due to the influence of relaxation rather than to coincidence.

If, as we assume, the essential feature in figure 5 as compared with figure 4 is that the subject relaxes the abdominal muscles more fully, this is attended by a markedly lower diastolic as well as systolic pressure. Although the decrement in tension, considering the musculature as a whole, is small, the reduction in pressure is marked.

A much greater decrement in microvolts, if it occurs when the subject is generally much more tense as shown by electrical measurements, may fail to be accompanied by such a marked lowering of pressure.

These results need to be confirmed. They suggest that blood pressure drops with muscle tension, but not proportionally; rather, the drop in pres-

sure is most marked if tensions have been previously reduced, especially if to the neighborhood of zero.

According to results so far considered, prolonged rest effects no marked reduction in pressure after the initial drop due to change of posture, not only if the subject remains more or less tense (while the variations in tension from time to time remain on about the same order) throughout the period (figures 2, 3 and 4); but also if he continues from the outset to be very well relaxed (figure 5). The intermediate condition, next to be considered, is where the subjects on the whole become more relaxed during the period or towards its close than they were at the outset. This condition probably occurs in most of the results considered in table 3, although an examination of the individual records falls short of furnishing proof that it prevails throughout the musculature of each subject.

Table 3 includes 10 subjects with normal blood pressure and four with essential hypertension. Only seven of the former group had been trained to relax; Ny and Ad were athletes belonging to University teams and were selected for the present studies after their ability to relax had been demonstrated in electrical tests.

We expect a fall of pressure in many or most instances in the first 10 or 15 minutes after lying down. The record of this preliminary fall is eliminated from table 3, since the initial reading is some 15 minutes or more after the change in posture. If after the pressure is thus lowered at the outset, a still further fall is found to occur with relaxation, even if not very large, it is likely to be significant since the amount of this fall added to the amount of the fall evoked upon change of posture may constitute a marked fraction of the pressure originally present before change of posture.

In the subjects with normal pressure, but not trained to relax, partial relaxation is attended by an average fall of about 5.6 and 7.2 millimeters respectively in systolic and diastolic pressure,* which is in addition to the initial fall effected upon change from standing or sitting to lying down. A somewhat greater average fall, namely about 12 or 13 millimeters both systolic and diastolic occurs in six instances out of nine in subjects with normal pressure but trained to relax; and a still greater average fall of systolic pressure in essential hypertension occurs in two out of three subjects partly trained to relax (namely about 22 millimeters). The number of tests represented in the studies of table 3 and table 4 is in a sense insufficient to warrant final conclusions, especially if these studies are considered apart from the other studies reported in the present and in following articles. However, careful inspection of the results in these tables nevertheless reveals a trend very clearly.

Figure 6 illustrates a record in hypertension. It is from the patient "Bh," observations on whom were discussed on page 1195. The influence

* This average includes only those instances in which a fall occurred and is based upon differences between the first and fourth readings. It should be noted that the analogous average from the "normal" untrained subjects in figure 2 has practically the same value.

TABLE III

Measurements of Blood Pressure and of Muscle Voltage in the Supine Posture, with Relaxation Generally Increasing

NORMAL BLOOD PRESSURE

Subjects not Trained	Date	Blood Pressure, mm.			Muscle Microvoltage				
		Before Rel.	After Rel.	Fall	0–15 Min.	15–30 Min.	30–45 Min.	45–60 Min.	60–75 Min.
Ny.[29] ♂	2/28/34	125/67	119/55	6/12	Arm: 0 to 0.5 (0.7)[1] Abd: 0.9 to 1.4	0 to 0.2 0.6 to 1.1	0 to 0.2 (3.0)[1] 0 to 0.6	0 to 0.2 (0.5)[2] 0 to 0.9 (1.4)[2]	0 to 0.2 (1.5)[1] 0 to 1.7
Ny.[29] ♂	3/14/34	127/75	125/70	2/5	Arm: 0 to 0.2 (9.8)[1] Quad: 0 to 0.7	0 to 0.2 (2.9)[1] 0.5 to 1.9	0 to 1.3 (4.3)[1] 0 to 0.8 (3.8)[1]	0 to 0.1 0 to 0.5 (5.2)[1]	0 0 to 0.7
Ad.[26] ♂	3/ 7/34	113/63	105/55	8/8	Arm: 0 to 0.9 (1.7)[1] Abd: 1.0 to 2.8	0 to 0.3 (2.3)[2] 1.8 to 2.5	0 to 0.3 1.2 to 2.2	0 0.8 to 1.8 (2.0)[2]	0 (2.3)[2] (3.4)[1] 0.8 to 1.5 (2.2)[2]
Ad.[28] ♂	3/14/34	118/61	113/63	5/−2	Arm: 0 to 0.4 (0.7)[1] (8.2)[1] Quad: 0	0 to 0.4 (13.3)[1] 0 to 0.7 (1.7)[4]	0 to 0.2 (8.7)[1] 0 to 0.7 (1.0)[2]	0 to 0.2 (9.3)[1] (13.3)[2] 0.3	0 to 0.2 0.3
Ba.[22] ♂	3/ 8/34	127/75	120/62	7/13	Arm: 0 to 4.6 Abd: 0 to 0.7 (1.0)[2]	0 0.7 to 1.3	0 (0.9)[1] 0.3 to 14.3 (20.0)[3]	0 0 to 4.3 (9.7)[2]	0 0
Trained									
Et.[31] ♂	3/ 3/34	137/90	129/77	8/13	Arm: 0 to 0.3 Eye: 12.0 to 19.0	0 9.0 to 13.0	0 8.0 to 15.0 (46.0)[1]	0 (0.2)[1] 4.0 to 19.0 (23.0)[1]	0 (0.3)[5] 8.0 to 15.0 (20.0)[1]
Et.[31] ♂	3/ 8/34	115/67	108/68	7/−1	Arm: 0 to 0.5 Eye: 6.0 to 13.0	0 to 0.5 6.0 to 8.0	0 to 0.5 5.0 to 9.0	0 to 0.5 (0.8)[1] 6.0 to 10.0	0 to 0.5 8.0 to 10.0
Et.[31] ♂	3/17/34	110/60	98/60	12/0	Arm: 0.3 to 0.5 Quad: 0 to 0.1 Eye: 5.0 to 15.0	0 to 0.5 0.3 to 0.1 2.0 to 9.0	0.3 to 0.5 (5.11)[1] 0.5 9.0 to 15.0	0 to 0.3 0 to 0.5 2.0 to 15.0+	0 to 0.3 0.2 to 0.6 4.0 to 15.0
Ro.[24] ♀	3/15/34	129/79	111/72	18/7	Arm: 0.5 to 4.4 Quad: 0.2 to 0.4 Eye: 18.0 to 34.0	0.3 to 1.2 0.2 to 0.4 10.0 to 16.0	0 to 0.9 (2.1)[1] 0.5 to 0.7 10.0 to 19.0	0.3 to 1.5 5.0 to 12.0	0.5 to 0.7 (4.2)[12]
Ka.[30] ♂	3/17/34	126/83	114/65	12/18	Arm: 0 to 5.8 Quad: 0.5 to 0.7 Eye: 14.3+	0.9 to 3.2 (5.4)[5] 0.7 to 1.0 14.3+	0.3 to 1.0 0.7 to 1.0 14.3+		
Lu.[27] ♂	3/14/34	132/88	135/88	−3/0	Arm: 0 to 0.2 Quad: 0 to 1.3	0 to 0.2 0 to 0.7	0 to 0.2 (0.4)[1] 0.3 to 1.2 (3.1)[1]	0 to 0.5 0.7 to 1.4 (6.3)[5]	0 to 0.2 0 to 0.7
Di.[37] ♂	3/ 1/34	138/80	128/75	10/5	Arm: 0.5 to 1.2 (2.5)[1] Abd: 0	0 to 0.3 0 to 0.2	0.3 to 0.9 (11.4)[2] 0	0.3 to 1.0 0	0.2 to 0.5 (4.1)[3] 0
Ve.[35] ♂	2/ 9/35	123/75	104/50	19/25	Arm: 0.5 to 1.0 (15.0)[1] Quad: 0.2 to 0.5 Abd: 0 to 0.5	0.3 to 0.5 0.2 to 0.5 0 to 0.5	0 to 0.4 0.2 to 0.5 0 to 0.5	0 to 1.1 (3.8)[3] 0.2 to 0.5 0 to 0.5	
Bn.[46] ♂	2/ 4/35	117/63	116/57	1/6	Arm: 0 to 0.2 (4.3)[3] Quad: 0.2 to 2.0 Abd: 0 to 0.2	0 0 to 0.4 0 to 0.2 (3.5)	0 0 to 1.2 0 to 0.4	0 0 to 0.5 0 to 0.4	

TABLE III (*Continued*)

ESSENTIAL HYPERTENSION

Not Trained	Date	Blood Pressure, mm.			Muscle Microvoltage				
		Before Rel.	After Rel.	Fall	0–15 Min.	15–30 Min.	30–45 Min.	45–60 Min.	60–75 Min.
Ch.[56] ♂	9/24/36	160/92	160/83	0/9	Arm: 1.0 to 2.3 (6.0)[1] (20.0)[10] Abd: 0.8 to 1.2 (2.8)[3]	1.0 to 4.0 (7.3)[1] 0.8 (1.2)[2]	1.0 to 4.3 (0.7)[2] 0.4 to 0.8	0.7 0.4 (0.8)[2]	0.7 (1.7)[2] 0.4 (0.8)[4]
Partly Trained									
Bh.[53] ♂	12/ 9/33	180/97	155/95	25/2	Arm: 0.3 to 3.0 Abd: 1.3 to 3.2	0.3 to 3.7 0.3 to 5.1 (15.0)[1]	0.5 to 1.5		
Be.[54] ♂	2/ 8/34	175/106	155/94	20/12	Arm: 0.3 to 3.2 Abd: 1.7 to 3.2 (15.0)[1]	0.2 to 6.3 1.3 to 2.4	0.2 to 3.6 0.5 to 2.0		
Ma.[51] ♂	1/12/34	172/82	165/68	7/14	Arm: 0.2 to 3.8 (5.8)[2] Abd: 1.3 to 4.2	0.8 to 1.4 1.1 to 2.7 (4.8)[1]	0 to 3.4 1.4 to 2.4 (3.5)[1]		

After stating the range in microvoltage in the last five columns, additional figures in parentheses denote variation from the range, where this occurred. Each coefficient denotes how many times the variation occurred. For example, since three determinations are made per minute, the coefficient "1" in the column, "30–45 Min.," indicates that the value in parentheses was determined during that period only once. The coefficient '*X*" denotes that the deviation was sustained practically constantly during the last portion of the period.

of fair relaxation is exemplified in the right arm flexor muscles during the first twenty-eight minutes; the pressure falls from 170 systolic and 87 diastolic (read after about 15 minutes lying) to 135 systolic and 80 diastolic. Pressure remains lowered and arm microvoltages do not increase much during conversation with him about an indifferent subject, the World's Fair. However, upon discussing the prospect of his aunt's death, about which he was greatly concerned, action potentials increase greatly in his arm muscles attended perhaps by a moderate rise in pressure, although the results here are not very marked. Upon resumption of chat about the World's Fair, the arm tensions diminish and perhaps the blood pressure somewhat also.

TABLE IV

Summary from Table 3.

NORMAL BLOOD PRESSURE

Subjects	Total Tests	No. Reduced	Aver. Reduction	Reduction in ¾ Cases
Not Trained	5	Systolic 5 Diastolic 4	5.6 7.2	
Trained	9	Systolic 8 Diastolic 8	9.3 8.8	13.3 12.3
ESSENTIAL HYPERTENSION				
Partly Trained	3	Systolic 3 Diastolic 3	17.3 9.3	22.5 7.0
TOTAL RESULTS				
All Tests	17	Systolic 16 Diastolic 15		

The results for subject Ch. are not included in this table.

However, after 45 minutes he begins to be concerned about a full bladder and his arm tensions mount conspicuously *; at 60 minutes the microvoltage exceeds 14. At this point the blood pressure has returned to the levels observed toward the start, terminating even slightly higher, 175 systolic and 90 diastolic. As will be noted, the increment of microvoltage from the arm muscles at the termination is out of proportion to the increment of blood pressure. This again illustrates the correlation discussed previously.

A control test in a patient with essential hypertension who fails to relax appears in figure 7. No decline is seen such as occurs with prolonged relaxation and the course of blood pressure is fairly irregular. Similar results were observed in two other hypertensive subjects.

* In another hypertensive individual disturbed by a full bladder, I have recorded a similar marked rise in pressure.

Comment

Since it is generally admitted that posture and emotion influence blood pressure, the aim in the present studies has been to render these influences constant so far as possible. Measurement of the neuromuscular elements has indicated that a quantitative relationship commonly prevails between the degree and duration of relaxation and the fall in pressure effected. However, this relationship is not a proportional one: generally speaking, under

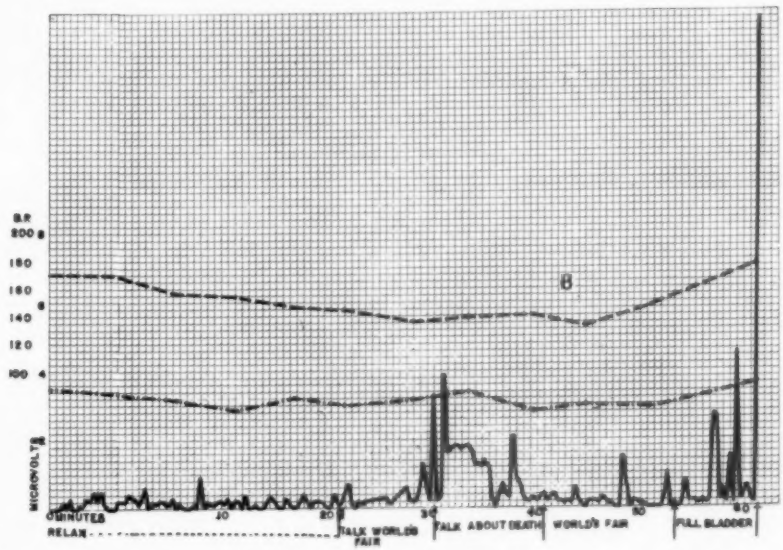

Fig. 6. Partial relaxation, moderate arterial hypertension, in a man 54, somewhat trained to relax. He has been resting for more than 15 minutes before the record is begun at "0 minutes." From 0 to 29 minutes of the record, relaxation in the right arm-flexors is fair, generally below ½ microvolt, with occasional peaks under 1. During this interval, blood pressure falls on the whole, from an initial 170/87 to about 135/80. In the period, 22 to 29 minutes, he converses about the World's Fair, evidently without becoming tense. From 29 to about 39 minutes, the investigator discusses with him a topic known to be exciting at the time, whereupon the action-potentials measured increase markedly, and there is perhaps some moderate corresponding increase in pressure, but this is not certain. With the decrease in action-potentials observed in the interval from 40 to 52 minutes, during which discussion concerning the World's Fair is resumed, a moderate decline in pressure probably again appears, but this decline, if present, most evidently gives place to the beginning of a marked rise in microvoltage as well as in pressure, evidently owing to sensations from a full bladder, about which he expressed mounting concern. While he finally becomes very tense, microvoltage above 14, the blood pressure increases markedly, but not proportionally.

present conditions, the fall in pressure which accompanies a slight decrease in tension becomes greater as relaxation becomes approximately complete.[10]

In accordance with the experience of most clinicians, we should expect a noteworthy drop in pressure to take place in the first 15 minutes of rest. This expectation was confirmed when the pressure was taken before the patient lay down to rest. We omitted taking the pressure during the first 15 minutes of rest because we did not wish to disturb the patient unnecessarily.

According to the present results, not merely systolic pressure varies with the state of skeletal musculature but diastolic pressure as well. Variation of diastolic pressure with the state of tension has been found not only with the Tycos instrument, but also upon auscultation with the stethoscope. Both diastolic and systolic phases have tended to fall with advancing relaxation. In general, the findings suggest that blood pressure tends to vary to a certain extent with the tension in the total mass of skeletal musculature; but the possibility remains that certain muscle groups are of particular moment, specifically the abdominal muscles.

If blood pressure varies with skeletal muscle tension and relaxation, this may conceivably be due to associated tension and relaxation of the muscle fibers in the arterioles and the muscular arteries. Lower pressure might

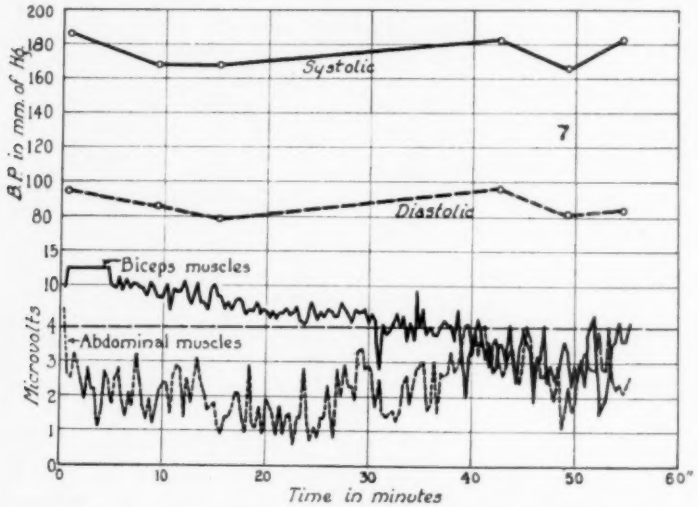

FIG. 7. Failure to relax, arterial hypertension, in a patient not trained to relax. The blood pressure remains up.

result from diminution of tonus, in the sense of Fritz Lange, as discussed above. Another mechanism might be reduction in the force and rate of the heart-beat brought about upon relaxation. Consideration of these possibilities is deferred to a later article.

There has been a traditional belief that healthy muscle, even at rest, is always in slight contraction. This view has rested upon inference. The present methods have afforded the first opportunity to test its accuracy; but have failed to confirm it. I have found in healthy man, as well as in animals, that action potentials (a sign of contraction) are completely absent in muscle fully at rest.[11]

SUMMARY AND CONCLUSIONS

1. It is known that blood pressure varies with emotion and with change of posture; but aside from casual clinical observations, no study to ascertain

whether blood pressure varies specifically with skeletal muscle tension has heretofore been made.

2. Quantitative studies of skeletal muscle contraction have been made possible through the development of very low voltage measuring apparatus. Some of the history of this development is recounted. Measurements were secured most commonly in the right arm flexor muscles, the abdominal muscles and the left quadriceps femoral.

3. Preliminary studies were made with the auscultatory method of taking blood pressure; later ones with the Tycos self-recording sphygmomanometer * in order to eliminate the subjective factor in taking blood pressure. To minimize the effects of change of posture upon the blood pressure recorded, the initial reading was not taken until the subject had reclined quietly for about 15 minutes.

4. Records were secured from 17 subjects with "normal" pressure not trained to relax, but while lying at rest. They confirm the findings in previous studies that individuals lying down do not necessarily relax; their various muscles may show varying frequencies and magnitudes of action potentials. During such moderate relaxation, no marked fall of blood pressure occurs.

5. Also, if there is marked failure to relax while reclining, the pressure does not fall.

6. The findings suggest that blood pressure tends to fall with decline in skeletal muscle tension, but not proportionally. The greatest fall, both systolic and diastolic, relative to the amount of tension relaxed, evidently occurs in the range where muscle contraction is slight and is then further reduced.

7. Under present conditions, blood pressure appears to remain approximately stationary during the rest period (beginning 15 minutes after change of posture), if the patient remains relaxed throughout, when it is at a relatively low level for that individual; but approximately stationary also, although at a higher level, if his muscles continue somewhat tense throughout and the fluctuations are not greatly at variance.

8. Greater falls in blood pressure, both systolic and diastolic, measured in millimeters often occur when relaxation takes place during or towards the end of the rest period, than when such relaxation is observed from the outset. No such fall commonly occurs in the hypertensive subject if he persistently fails to relax.

9. An initial drop in pressure commonly follows change to the lying posture. Thereafter an additional fall in pressure often occurs, evidently due to relaxation. The sum of these two decrements may constitute a considerable percentage of the initial pressure—a consideration which adds weight to the figure for the fall effected upon relaxation.

* The systolic readings with this instrument are probably more reliable than are measurements made with the aid of the stethoscope. Unfortunately, the diastolic measurements with this instrument have not been standardized; however, for the comparative purposes of the present studies, they appear to be fairly satisfactory.

10. The findings furnish foundation for the view that high blood pressure in essential hypertension can result in part from habitual activity involving hypertensive states in the skeletal musculature.

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HUMAN AUTONOMIC PHARMACOLOGY

XV. THE EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL) BY IONTOPHORESIS ON ARTERIAL HYPERTENSION *

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IN previous experiments [1, 2] on the pharmacology of the autonomic nervous system, it was found that the blood pressure elevation produced by benzedrine sulfate (benzylmethyl carbinamine or beta-phenyl-isopropyl-amine) was quickly lowered by an injection of mecholyl (acetyl-beta-methyl-choline chloride). This effect was of short duration, the blood pressure quickly resuming the high level produced by the benzedrine.

In the present study, our aim was to compare the blood pressure lowering effect of mecholyl iontophoresis on benzedrine-induced hypertension and on senile hypertension.

The technic of mecholyl iontophoresis has been described by many authors, including ourselves.[3, 4, 5, 6, 7] The drug is introduced into the organism via the skin by means of the galvanic current through the positive electrode saturated with 1 per cent mecholyl solution at a milliamperage varying from 5 to 30. The strength of the current is varied, according to the reaction of the individual subject to mecholyl. In most instances, the positive electrode was applied to the abdomen and the negative electrode to the back; in others, the thigh or the leg was used. Wire gauze electrodes enclosed in flannel bags were found most convenient, since they readily conformed to the contour of the part to which they were applied. Greater absorption of the mecholyl seemed to occur over the abdomen than on the thigh or leg. When the iontophoresis was continued for longer than one hour, the electrodes were resaturated with the mecholyl and salt solutions respectively.

The experiments were carried out on the following groups of subjects: (1) a group of 10 dementia praecox subjects whose cardiovascular systems were apparently normal and in whom a hypertension was produced by intramuscular injections of benzedrine sulfate (40 to 50 mg.); (2) a group of 8 senile subjects exhibiting varying degrees of hypertension; and (3) a group of 7 senile hypertensives in whom the iontophoresis was preceded by the administration of prostigmin (dimethylcarbamic ester of *m*-oxyphenyl-trimethylammonium methylsulfate), 0.5 mg. subcutaneously.

* Received for publication November 13, 1937.
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Results

1. *Effect of mecholyl iontophoresis on the hypertension produced by benzedrine:* Table 1 gives the important data in regard to the blood pressure

Table I

The Effect of Mecholyl Iontophoresis on the Hypertension Produced by Benzedrine

(10 Cases of Dementia Praecox)

Case	Before Iontophoresis				Period of Iontophoresis			After Iontophoresis	
			Ht. of Benzedrine Reaction		Ht. of ABC* Reaction			(Within 2 minutes)	
	Initial B.P.	Pulse	B.P.	Pulse	Minimum B.P.	Time†	Pulse	Final B.P.	Pulse
G. T.	124/80	64	184/90	54	136/70	60 min.	88	158/88	64
J. M.	156/90	88	214/104	64	156/92	60 "	100	200/108	68
L. G.	98/66	68	160/95	56	122/78	90 "	64	150/90	54
G. T.	134/82	68	176/88	60	144/68	30 "	88	162/90	60
L. G.	100/60	78	158/98	60	100/50	75 "	100	140/88	56
M. G.	130/88	84	200/110	68	120/80	57 "	108	190/102	62
A. W.	130/66	96	152/70	76	116/50	30 "	108	148/70	76
E. J.	136/90	84	178/98	70	152/84	30 "	84	174/100	64
J. G.	120/72	56	180/100	56	140/82	35 "	88	170/106	66
A. McN.	116/80	86	150/96	76	120/82	37 "	84	144/96	72

* Acetyl-beta-methylcholine chloride (mecholyl).
† Length of time normal blood pressure maintained.

and pulse changes in this group of experiments. (*a*) The basal blood pressure of the 10 subjects ranged from 98 mm. of mercury systolic and 66 diastolic (98/66) to 156 mm. systolic and 90 diastolic (156/90). The maximum blood pressure readings, following the administration of benzedrine, varied from 150/96 to 214/104, with an average systolic rise of 51 mm. and an average diastolic rise of 19 mm. Accompanying these changes in blood pressure, there was a fall in pulse rate in nine of the cases, varying from 8 to 24 beats per minute; in the other case, no change in pulse rate occurred. (*b*) The fall in blood pressure during the period of mecholyl iontophoresis was gradual and reached its lowest levels in from 13 to 56 minutes. The decrease in pressure varied from 26 to 80 mm. systolic and from 12 to 48 mm. diastolic, with an average systolic decrease of 45 mm. and an average diastolic decrease of 21 mm. During the period of reduced blood pressure, the pulse showed an average increase of 27 beats per minute, varying from 8 to 40 beats per minute. In only two cases did the pulse go above 100; in all instances, it remained regular and of good quality. Once the blood pressure had reached a low level, the iontophoresis was continued from 30 to 90 minutes, maintaining a normal or low level of blood pressure readings

during that time. Upon cessation of the current, the blood pressure returned to previous levels in from 5 to 15 minutes. In most instances, there occurred flush and mild perspiration of the face and sometimes of the chest, slight lacrimation, and audible intestinal peristalsis. Until these phenomena occurred, there was little or no effect on the blood pressure. Iontophoresis with mecholyl was regularly effective in lowering the hypertension produced by benzedrine to normal levels. In two cases, furthermore, the iontophoresis applied before the administration of benzedrine prevented a rise in blood pressure so long as it was continued (charts 1 and 2).

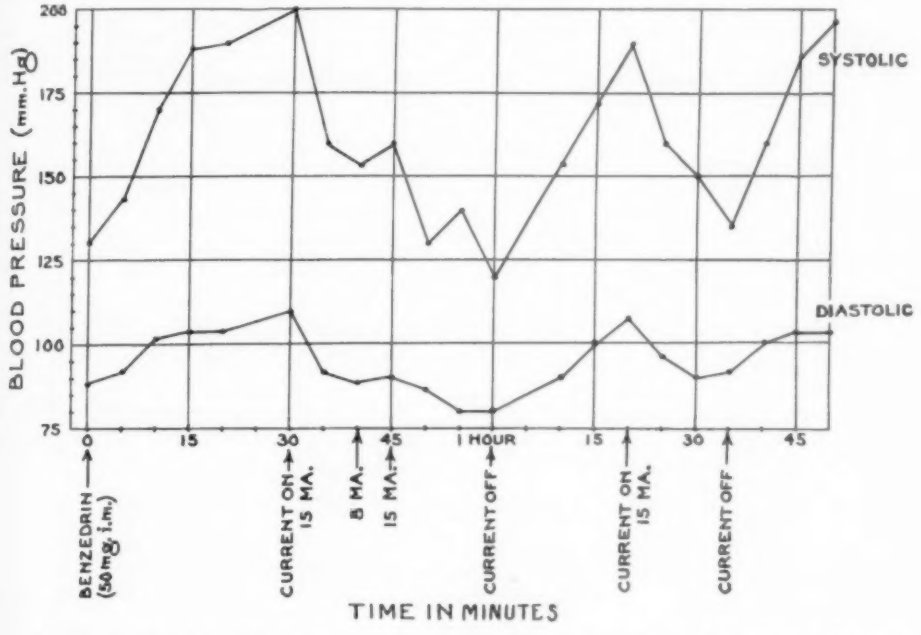

CHART 1 (Case M. G.): The effect of mecholyl iontophoresis on the hypertension produced by benzedrine. The blood pressure was very effectively reduced to normal levels and quickly returned to a high level when the current was discontinued.

2. *The effect of mecholyl iontophoresis on eight subjects with senile hypertension* (table 2, charts 3 and 4): These subjects varied in age from 70 to 75 and showed both retinal and peripheral sclerosis. The basal blood pressure readings ranged from 176/86 to 214/120. In five of these subjects, prolonged iontophoresis reduced the systolic blood pressure from 30 to 70 mm. of mercury, and the diastolic pressure from 10 to 30 mm. of mercury, so that both the systolic and diastolic readings reached normal or approximately normal levels in three cases. In the other two cases, the blood pressure was significantly reduced but not to normal. As in the previous group of subjects, the pressure remained at minimum levels as long as the current was applied and returned to or close to their original readings within a short time after the current was discontinued.

Of the other three cases, the reduction in pressure was as follows: Two of these subjects showed an interesting phenomenon—although the blood pressure fell close to normal levels at times, wide fluctuations occurred, so that high readings alternated with the minimum readings. In the third case, a negligible fall in blood pressure occurred.

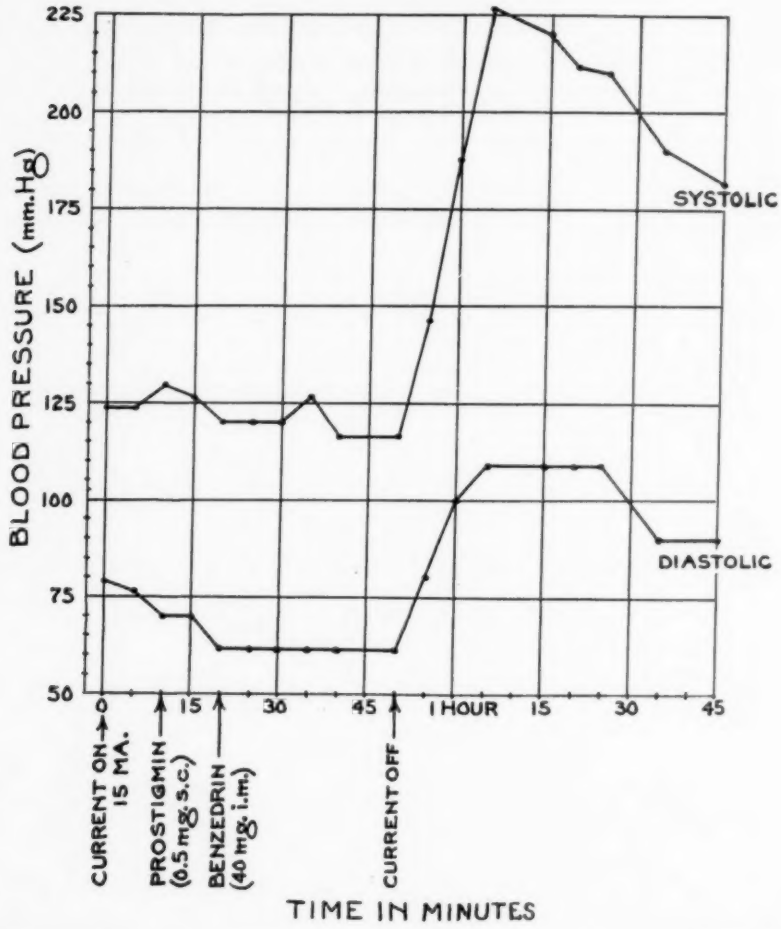

CHART 2 (Case G. T.): The counteracting effect of mecholyl iontophoresis preceded by prostigmin on benzedrine hypertension. The blood pressure remained unchanged for 30 minutes after the benzedrine injection, then quickly rose when the iontophoresis was discontinued.

The pulse rate in four of the eight cases showed either slight or insignificant changes. When the blood pressure had returned to the original level following the cessation of the iontophoresis, a significant fall in pulse rate occurred in four cases. Throughout the experiments the pulse showed no unusual rhythm or change in quality.

No correlation could be made between the state of the peripheral vessels

TABLE II

The Effect of Mecholyl Iontophoresis on Senile Hypertension

(8 Cases)

Case	Before Iontophoresis		Period of Iontophoresis			After Iontophoresis	
	Initial		Ht. of ABC* Reaction			Final	
	B.P.	Pulse	Minimum B.P.	Time†	Pulse	B.P.	Pulse
P. F.	184/90	76	146/70	45 min.	80	172/80	72
P. W.	194/96	80	174/106 148/88	—	88	190/118	68
A. W.	214/120	68	184/110	10 "	68	220/126	68
H. R.	190/110	60	186/100 140/80	—	72	200/110	60
D. S.	200/110	104	158/80	38 "	104	196/116	96
E. M.	176/86	60	144/70 110/62	43 "	64	178/90	60
J. B.	196/106	72	142/88 126/76	45 "	68	200/110	68
A. S.	210/108	60	200/108	—	72	240/120	76

* Acetyl-beta-methylcholine chloride (mecholyl).
† Length of time normal blood pressure maintained.

and the fall in blood pressure. For example, one subject, with very hard and beaded radial vessels, showed an ideal response to the iontophoresis. In two cases, in which a marked blood pressure response occurred, the radial arteries, which felt thick to the fingers before the experiment, felt normal when the blood pressure reached a non-hypertensive level.

No evidence of any special discomfort or untoward signs occurred in any of the eight subjects; flush of the face and sometimes of the chest, with mild sweating, occurred in every case. Increased desire to urinate and audible intestinal peristalsis were present in the majority of the subjects.

3. *The effect of mecholyl iontophoresis preceded by the administration of prostigmin* (table 3, chart 4): Four senile hypertensives, three of whom had had an unsatisfactory fall in blood pressure with mecholyl iontophoresis alone and three other senile subjects were given subcutaneous injections of prostigmin (0.5 mg.) 5 to 15 minutes prior to the mecholyl iontophoresis. Prostigmin was administered because it is a marked synergist to mecholyl in modifying the autonomic functions of the body, including the sweat production, the regulation of blood pressure, the gastric secretion and the bladder tonus. The three subjects who responded unsatisfactorily to the administration of mecholyl iontophoresis alone and one other subject will be considered briefly:

(1) *Case H. R.:* This patient had a basal blood pressure of 210/110. Prostigmin (0.5 mg. s.c.) by itself was without effect, but followed by

mecholyl iontophoresis produced a gradual fall in 15 minutes to 140/70. These readings remained approximately stationary for 15 minutes, when the current was turned off to allow the patient to urinate. Following this, the blood pressure returned to a level of 210/105. Renewal of the iontophoresis caused a fall in blood pressure to 178/90 within 15 minutes. At this point the current was discontinued because of the patient's marked restlessness. In a previous control experiment, the same patient had been given iontophoresis without prostigmin and showed a fall in blood pressure

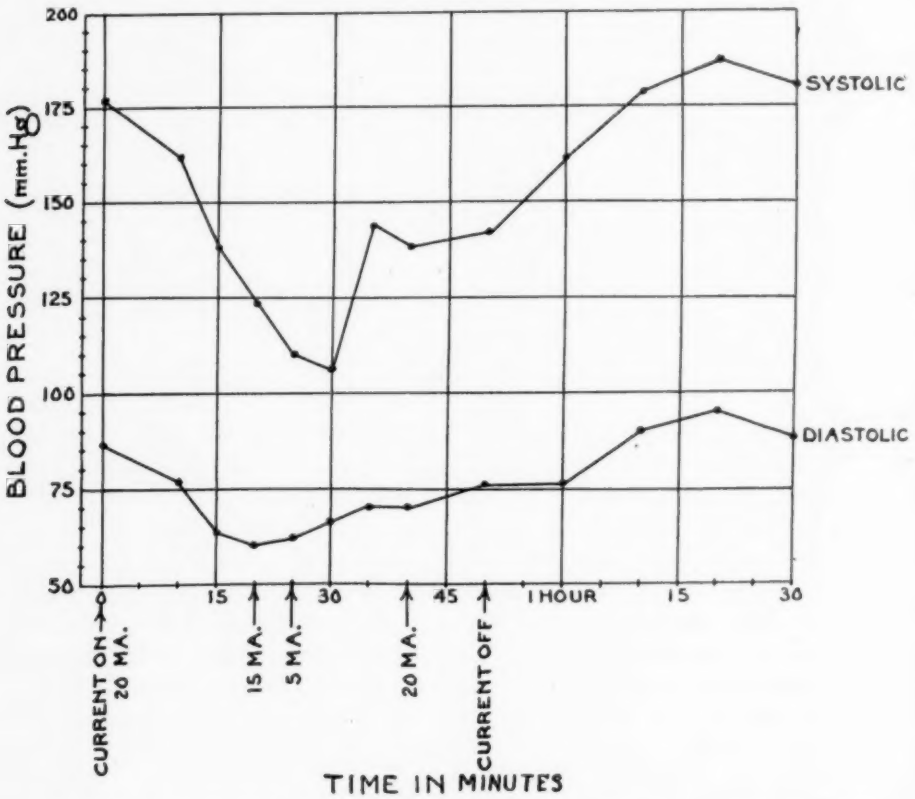

CHART 3 (Case E. M.): The effect of mecholyl iontophoresis on senile hypertension. The blood pressure was kept at a non-hypertensive level for about 43 minutes and returned to its initial high level after the current was discontinued.

from 190/110 to 140/80. These changes, however, could not be maintained; there was an alternation of a fall and rise between 140/80 and 186/100 during the iontophoresis.

(2) *Case P. W.:* This subject had very hard, tortuous radial vessels. When mecholyl alone was introduced by iontophoresis, there was a fall in blood pressure from the original reading of 194/96 to 148/88, the reduction being intermittent and ranging between the latter reading and 174/106.

When prostigmin was given subcutaneously, followed by iontophoresis, the blood pressure fell from 174/104 to 136/78 within 8 minutes, rose to 148/80 and remained at this level for 43 minutes.

(3) *Case A. S.* (Chart 4): By iontophoresis with mecholyl alone a negligible drop in blood pressure, from 210/108 to 200/108, occurred, using up 32 milliamperes of current over a period of 43 minutes. Sweating and flushing of the face occurred, showing that the drug was being introduced

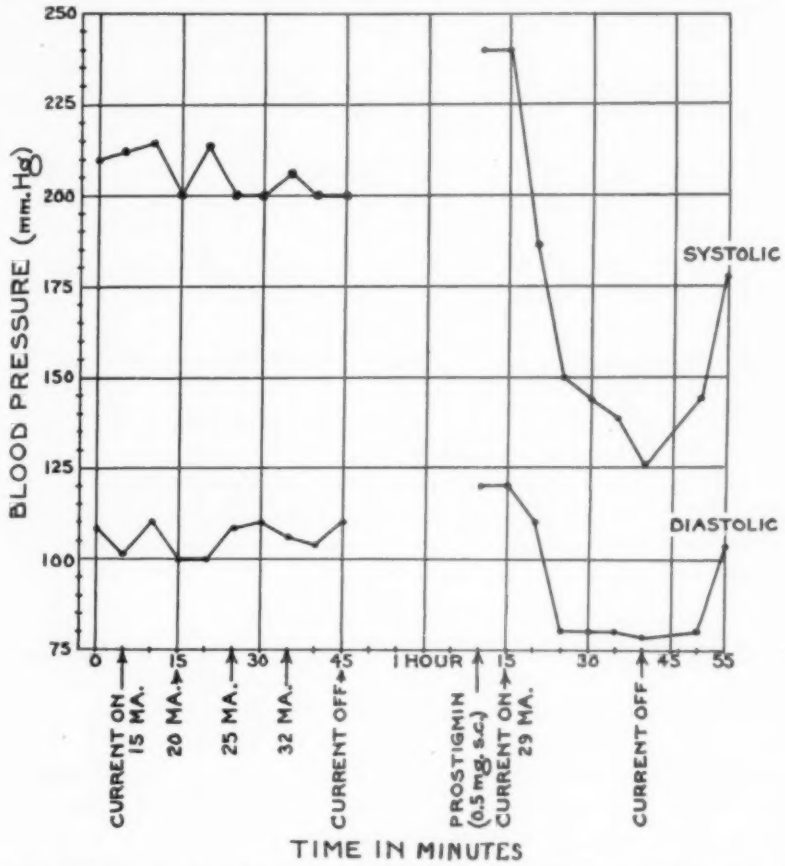

CHART 4 (Case A. S.): The effect of mecholyl iontophoresis on senile hypertension. Iontophoresis alone was ineffective, but when combined with prostigmin the blood pressure fell to a normal level where it remained until the current was discontinued.

in " physiological " amounts. Upon cessation of the iontophoresis, the blood pressure rose to 240/120 within the subsequent 25 minutes. At the end of this period, prostigmin (0.5 mg. s.c.) was administered and mecholyl by iontophoresis again given 5 minutes later. The blood pressure now fell steadily to 126/76 during the ensuing 20 minutes, with a current milliamperage of 20. Upon cessation of the current, the blood pressure quickly rose to 180/104. In the course of the iontophoresis, the patient urinated

twice, passing on one occasion 500 c.c., and on the other 300 c.c. The radial arteries, which seemed to be thick and hard at the beginning of the experiment, felt normal when the blood pressure was at its minimum.

(4) *Case J. B.:* This patient also showed a more satisfactory reduction in blood pressure when mecholyl iontophoresis was preceded by prostigmin than when mecholyl iontophoresis was employed alone. With the combination of drugs, he showed a fall in blood pressure from 196/104 to 110/64 within 12 minutes following the introduction of mecholyl by iontophoresis. Only 8 milliamperes of current were required to obtain this reaction. The minimum blood pressure was maintained at approximately the same level for 30 minutes, when the experiment was discontinued because of the patient's desire to defecate. Throughout the period of mecholyl iontophoresis the pulse remained at the rate of 60 and continued strong and regular. Twelve minutes after the current had been discontinued, the blood pressure returned to a level of 210/100. During the time the blood pressure was at its minimum, the radial vessels, which were moderately thickened originally, became soft. In a previous experiment, the same patient had been given mecholyl iontophoresis alone with a current of 25 milliamperes, as a result of which the blood pressure showed a satisfactory reduction, namely, from 196/106 to 126/76. There were fluctuations ranging between this latter level and 142/88 for a period of 45 minutes, at which time the current was discontinued.

The four other senile hypertensives, who received injections of prostigmin (0.5 mg. s.c.) preceding mecholyl by iontophoresis, showed very satisfactory reductions in blood pressure which were maintained as long as the current was continued (table 3).

TABLE III

The Effect of Mecholyl Iontophoresis on Senile Hypertension when Preceded by the Administration of Prostigmin (0.5 mg. s.c.)

(7 Cases)

Case	Before Iontophoresis		Period of Iontophoresis			After Iontophoresis	
	Initial		Ht. of ABC* Reaction			Final	
	B.P.	Pulse	Minimum B.P.	Time†	Pulse	B.P.	Pulse
J. P.....	178/108	108	110/70	47 min.	92	168/112	76
J. P.....	166/106	80	122/74	40 "	80	172/104	64
H. R.....	210/110	60	140/70	25 "	72	210/105	52
P. W.....	174/104	80	136/78	43 "	88	174/100	72
A. S.....	240/120	64	126/76	28 "	60	180/104	60
J. B.....	196/104	68	110/64	30 "	60	210/100	56
E. McC..	178/90	64	138/70	18 "	72	230/110	58

* Acetyl-beta-methylcholine chloride (mecholyl).
† Length of time normal blood pressure maintained.

Comments

It is probable that the mechanism by which benzedrine sulfate causes a hypertension is relatively simple compared to the mechanism by which essential or senile hypertension is brought about. The ability of acetyl-beta-methylcholine chloride, introduced by the method of iontophoresis, to overcome the vasoconstricting action of benzedrine, and thus produce a fall in the elevated blood pressure as long as the drug continues to be absorbed, is uniformly seen in the experiments noted herein. On the other hand, by mecholyl iontophoresis alone it is often difficult to lower the hypertension of senile subjects to normal levels. The failure in the latter cases may be due to the incapacity for dilatation of the arteries and arterioles and perhaps to the presence of high amounts of cholinesterase in the body, or to both causes. From the present experiments, no definite aid in explaining the failures is obtained from the state of the radial vessels, for satisfactory reductions in blood pressure occurred in instances in which the peripheral vessels were very tortuous or hard.

The injection of prostigmin preceding mecholyl iontophoresis definitely enhances the effect of the latter drug, as shown by the effect of both drugs on the seven senile hypertensives. Whether this synergism is accomplished by the destruction of the cholinesterase in the tissues, thus rendering the mecholyl more effective, or whether the prostigmin acts in some other manner is not known. In those cases in which the combination of prostigmin and mecholyl iontophoresis failed to effect a satisfactory reduction in blood pressure, there may have been too many arterioles so damaged as to be incapable of dilatation.

Summary and Conclusions

1. In 10 young dementia praecox subjects, the hypertension produced by benzedrine sulfate was markedly reduced to normal or close to normal levels for periods varying from 30 to 90 minutes, that is, as long as the drug was allowed to be absorbed.

2. In three of eight senile hypertensives, the blood pressure was markedly reduced to normal or close to normal levels for varying periods of time.

3. In all of seven senile hypertensives, the administration of prostigmin prior to the mecholyl iontophoresis produced a reduction in blood pressure to normal levels. Three of these patients had failed to respond satisfactorily to iontophoresis alone. This suggests the possibility of a "hyperesterasia" which may play an important rôle in the production of hypertension.

4. No untoward effects were noted during the mecholyl iontophoresis. The rate of absorption of the drug is readily controlled by regulating the milliamperage, so that the blood pressure may be very gradually lowered. Only slight discomfort, consisting of flushing, mild sweat, slightly increased intestinal peristalsis, and desire to urinate are produced by the method.

The mecholyl used in these experiments was generously supplied by Merck & Co., the benzedrine sulfate by the Smith, Kline & French Laboratories, and the prostigmin by Hoffmann-LaRoche, Inc.

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LOW CHEST AND UPPER ABDOMINAL PAIN *

By Wm. M. Ballinger, A.B., M.D., F.A.C.P., *Washington, D. C.*

Severe pain in the lower chest and upper abdomen is a symptom common to many affections involving several different systems of the body. Cardiovascular disease, respiratory disease, lesions in the upper gastrointestinal tract as well as certain lesions of the central nervous system may frequently produce pain in the upper abdomen or lower chest or both. Thus pain in the lower chest may be due to disease of the heart, lungs or pleura on the one hand, or it may be caused by gastrointestinal lesions alone. Likewise upper abdominal pain may be due to disease located either below or above the diaphragm. This state of affairs naturally leads to confusion and error in diagnosis but with treatment varying radically according to the origin of this type pain the importance of accurate diagnosis is apparent. With this in mind some of the more common causes of low chest and upper abdominal pain will be discussed together with a few illustrative case reports.

Of the cardiovascular affections, coronary disease ranks first in the production of low chest or upper abdominal pain. Acute coronary occlusion is the most severe if not the most frequent manifestation of coronary disease.[1] An acute coronary occlusion is typically ushered in by persistent severe pain beneath the sternum, usually radiating to the shoulder girdle and often down one or both arms. However, this radiation may be downward into the epigastrium or over to the liver and gall-bladder area; or occasionally into the lumbar back. Again, in less typical attacks the severest pain may be localized beneath the tip of the ensiform while in some cases nausea and vomiting together with epigastric fullness and discomfort are more pronounced than any chest pain. Particularly in these atypical cases it is the accompanying history, signs and symptoms that may lead to a correct diagnosis.

Such a case is that of a priest, 78 years of age, who had been hospitalized for some months following an amputation of his right leg for diabetic gangrene. He had made a complete postoperative convalescence but because of his age, his diabetes and the coincident generalized arteriosclerotic changes, had remained in the hospital to receive general diabetic care. One morning he complained of sudden epigastric distress with mild nausea. This same ill feeling had been noted intermittently and quite irregularly for a week or ten days prior. However, this attack was much more severe and was accompanied by a feeling of marked prostration, mild sweating and an immediate irregularity of the pulse. Several hours later he was much more comfortable but still unusually prostrated and his pulse remained irregular and somewhat faster than his average. On the following day he was better but still ill at ease, weak and somewhat apprehensive. Blood pressure at this time was 102 mm. of Hg systolic and 85 diastolic, as contrasted with his average of 126/80. Pulse now slowed to 70–80 per minute but still quite irregular. The following day a degree or two of fever was noted and a leukocyte count showed 11,500 cells. The fever and

* Read before the Post-Graduate Clinic, Georgetown University College of Medicine, September 15, 1937.

the leukocytosis remained another two days and then gradually came down to normal. During this time there was nothing remarkable to be heard on auscultation over the heart, except the irregularity. This persisted until a 2 to 1 block was apparent and finally a complete block with heart and pulse rate of 26 to 29. This latter was short-lived, however, and quickly a 2 to 1 rate was resumed. Electrocardiographic studies showed typical evidence of myocardial infarction and follow-up electrocardiograms were continued over a period of months until finally a complete return to normal was noted. Clinical recovery of course was apparent some time before this.

This case report illustrates the atypical variety of acute coronary occlusion in which diagnosis is based on observation of factors other than pain alone.

However well known the symptoms of a typical occlusion, it may be proper to briefly review them. Besides the pain which is usually most severe and unrelenting, the patient so affected is quite apprehensive, apt to be restless, changing position, moving from chair to bed and around the room. His skin is pale and sweaty such as is seen in minor degree of shock. Pulse rate is increased. Not infrequently some irregularity in rhythm may be noted. Dyspnea is present; it is usually of moderate degree only. Likewise slight cyanosis may be present. Dyspnea and cyanosis are ordinarily not marked but form a rough index of the efficiency of the circulatory apparatus. If myocardial damage has been severe, dyspnea and cyanosis will be more prominent. In an occasional case dyspnea may be the most prominent symptom from the beginning. Physical examination during the attack is usually not diagnostic of itself but may add considerable support for or against the presence of thrombosis in the given case. Blood pressure falls at first to below average for the individual, then gradually returns to normal after the acute phase of the attack has passed. Temperature early is normal or sub-normal but after an interval of a day or two a low grade fever develops usually not more than 101° or 101.5° F. The heart may be found to be normal in size and position and free of murmurs or occasionally some enlargement may be detected with or without a mitral or aortic murmur. Rigidity of the upper abdominal muscles with some accompanying tenderness may be present. This is confusing only if the other accompanying symptoms and physical signs are lost track of. With the fever a leukocytosis develops, usually from 12,000 to 20,000. Occasionally a pericardial friction rub may also be detected at this time, some two to four days after the onset. This pericardial friction rub does not occur commonly but when present constitutes the most certain diagnostic sign that may be elicited by physical examination. Experienced clinicians generally recognize a slightly muffled quality or indistinctness of the heart sounds during an attack of acute occlusion. The heart sounds seem distant and are not as clear-cut as normal. The history in these cases of coronary thrombosis usually reveals the onset of the attack while the individual was at rest. The patient is nearly always in the arteriosclerotic decades of life and a past history of hypertension or

of anginal attacks lends considerable evidence in favor of a thrombosis. Another noteworthy feature in these cases is the marked prostration and ready fatigue which follow the attack and which persist for weeks or months. Finally an electrocardiogram made usually the sixth or seventh day after the onset of the attack will show changes typical of the condition. If serial electrocardiograms are made their diagnostic importance is increased.[2]

First cousin to coronary thrombosis in symptoms and etiology is angina pectoris, since both affections are due to interference with the coronary circulation and to the presence of some degree of coronary sclerosis.[3] The anginal pain may be at first indistinguishable from that of actual thrombosis; but in the former the interference with coronary circulation is temporary while in the latter it is permanent, and the clinical course varies accordingly. Anginal pain is a matter of seconds or minutes while that of thrombosis is of minutes, hours or even days. Anginal attacks are precipitated by greater than average exertion, either physical or emotional, while attacks of thrombosis are not so directly related to either. Of course anginal attacks may and often do, precede an actual occlusion but in such a case both the patient and the doctor usually realize that there has been a more serious, more prolonged and more disastrous turn in events. The patient with a typical anginal attack is nearly always seized while in the midst of some physical or emotional or nervous activity. During the attack he remains peculiarly and strikingly still wherever he may be at the time of the onset. He is usually quite apprehensive. Physical examination shows normal pulse, blood pressure and heart sounds. The attack is soon over and fever and leukocytosis do not follow.

Coronary disease is responsible for still another group of cases presenting low chest or upper abdominal pain as their chief symptom. This is the group of early coronary sclerosis with neither frank anginal nor thrombotic manifestations but who complain of discomfort after eating or after moderate exercise or both.[4] This group is perhaps of more importance relatively than any other because it includes those cases in which the diagnosis is most often missed and in which an accurate diagnosis at this stage would be of greatest benefit to the patient. These patients are regularly treated for indigestion and all too often die of an acute coronary occlusion or sudden myocardial failure and are listed by our daily press as victims of "acute indigestion." Patients in this group are in the arteriosclerotic age, usually past 50, often past 60 years of age. Physical and laboratory examination are productive of little or nothing out of the normal. It is the careful history that discloses the true nature of the case. Distress, fullness, epigastric discomfort, aerophagia and belching are the symptoms that lead these folk to seek relief from indigestion but close questioning shows that these symptoms develop only when some extra load is thrown on the circulatory apparatus, typically when some even quite moderate exertion is attempted soon after a meal. Usually the symptoms are more

marked if fatigue is present and therefore it is commonly the evening meal that produces the most distress, also because the evening meal may be the heaviest. However, symptoms do not necessarily immediately follow a meal.

Such a case was M. S., a man past 60, who complained of a distress which was localized definitely in the epigastrium. This distress was described as a feeling of heaviness which appeared at fairly regular intervals, particularly after the midday meal. Because of the location and periodicity of the distress a diagnosis of duodenal ulcer had been made. Upon questioning it was learned that the discomfort was seldom experienced except after his lunch. Further it was found that this patient was in the habit of walking to his office about one hour after his lunch and that it was during this time that the distress was usually noticed. He had already observed that the pain promptly subsided after he had reached his office and that he might obtain relief by resting on the way. Still further questioning showed that this man could literally eat peanuts, popcorn and crackerjack without digestive distress but that his symptoms developed only when the extra circulatory load of exercise was added to that of digestion.

There is great variation in the symptoms presented in this group of early coronary sclerosis but the significant facts which may be brought out by careful questioning are: first, that ordinarily speaking digestion per se is good; second, that symptoms appear only when a load of some kind is placed on the circulatory system; and third, that simple rest has been found most effective in relieving the symptoms.

Closely allied to these coronary types is a group of patients in whom upper abdominal pain results from interference with circulation in the upper abdominal vessels themselves.[5] These are variously classified as cases of intermittent claudication and abdominal angina.[6] They are recognized by the absence of other organic disease which might explain the pain present and by the pertinent history that they occur only when there is an increase in the circulatory load of these vessels, that is after meals and especially after heavy meals.[7] Fatigue is a frequent predisposing factor. Their occurrence may be intermittent or rhythmic, in the latter case suggesting strongly the presence of gastrointestinal disease. They occur almost without exception in the latter decades of life when arteriosclerosis becomes manifest. However, an occasional case of pure vascular spasm in much younger individuals has been reported. In passing it is noteworthy that the condition of the peripheral arteries is seldom an index to the absence or presence of atheromatous and sclerotic changes in the heart and viscera.

Heart failure from whatever cause, if of relatively sudden onset may produce severe upper abdominal pain with nausea and vomiting.[8] Likewise acute pericarditis may commonly be ushered in with severe low chest and upper abdominal pain accompanied by nausea and vomiting, tenderness and rigidity.[9] The differentiation in this latter condition is made by first suspecting the true condition present, by hearing a pericardial friction rub and later by the presence of pericardial effusion.

The next large group of cases presenting upper abdominal and often

low chest pain as their prime symptoms are those due to disease of the gastrointestinal tract.

The esophagus is a rather silent uncomplaining organ and yet it is not infrequently the offender in pain beneath the sternum. For some reason it is rarely thought of in our consideration of possible causes of this type of distress and for this very reason diagnoses may be missed.[10] Inflammation, ulceration, diverticula, tumors and simple spasm of the esophagus occur with regularity and each may produce pain. The cardinal symptoms in esophageal disease are distress beneath the sternum, and difficulty in swallowing. The distress may be only a feeling of pressure or of constriction, or may be actually painful as a burning sensation, or may be more severe as a boring or steady pain. The significant point is that it is always aggravated by the act of swallowing. When organic disease is present, such as ulcer or tumor, coarse food or a large bolus of food will produce the most discomfort; while in simple spasm iced drinks usually cause the most discomfort. Warm, demulcent, soft foods usually are soothing and relieve the distress to a greater or less degree regardless of cause. The difficulty in swallowing, or dysphagia, is often described as a feeling as though food or liquid stopped or lodged at a certain area and there is a perceptible time interval before it passed into the stomach. Often several swallows are necessary to move the bolus through. Sometimes it may be regurgitated if the obstruction is great.

Last month a woman was seen suffering with a burning pain beneath the lower sternum, continuous but much aggravated by the swallowing of food or liquid. She was in a hospital following delivery of an infant just four days before. Because of the severity of the pain, its location, and its duration the intern on duty suggested that she had a coronary thrombosis. However, upon questioning it was found that her anesthetic had been unusually prolonged at the time of delivery and that this substernal discomfort was noted almost as soon as she had regained consciousness. Because of the typical character of her distress and the absence of any other signs or symptoms, a diagnosis was readily made of post-anesthetic esophagitis. This was borne out by the rapid disappearance of her pain when she was placed on a diet of gruels and other soft, warm, demulcent food exclusively.

Diaphragmatic hernia is another cause of pain in the epigastrium and lower chest and one which is difficult to discover.[11] These herniae may occur at any age and give symptoms of mild dysphagia, low chest discomfort, pressure, sometimes burning usually following a meal. All symptoms are aggravated by lying down soon after eating and are relieved by assuming the upright position. Many of these cases have chronic blood loss from petechial hemorrhage or from actual ulceration at the area of herniation and on examination are found to have a marked hypochromic type anemia. The diagnosis in these cases is suspected from the history but proof of their existence depends on their recognition during roentgen-ray study at which time the patient's head and shoulders are tipped down so that a marked Trendelenburg position is assumed.

Ulceration of the gastric mucosa close to the cardia, like ulcers at or just

above the cardia in the gullet, usually produces pain high in the epigastrium or beneath the lower sternum or xiphoid. Although the symptoms are typically ulcer-like yet the difficulty in diagnosis is the fact that this area in the stomach is the most difficult of all to visualize either by roentgen-ray or by gastroscope. The chronicity of the pain, its periodicity and its location should make one suspect the presence of an ulcer in these cases. Another significant feature here is the effect of position on the discomfort. Patients with ulcers high along the lesser curvature are usually much more comfortable in an upright position than in a reclining one. One such patient had gone to the trouble of building a back rest in his bed so that even in his sleep he would remain semi-upright. Ulcers in this location, as well as those close to the pylorus, require constant observation because of the high incidence of carcinoma. Simple uncomplicated peptic ulcers do not give sharp or well localized pain. However, when they begin to penetrate deeper into the wall or when they perforate, with accompanying peritoneal irritation, then the character of pain changes, becoming much sharper, more constant, better localized and often radiating according to their location, up or down or to one side. Those with radiation of pain into the lower chest sometimes present problems of diagnosis coming within the scope of this paper.[12] They are to be recognized because of the past history of more typical ulcer symptoms and the presence of well localized tenderness and muscle rigidity which accompanies penetration or perforation. Direct visualization of the esophagus and stomach, together with the older more generally used methods of examination should demonstrate fully 95 per cent of all lesions occurring in these organs.

However, the gastrointestinal lesions which cause the greatest confusion in their diagnosis are those acute episodes associated with perforation of an abdominal viscus, an acute biliary colic, or an acute pancreatitis. When Paul White of Boston [13] and the late Harlow Brooks of New York,[9] two of the country's outstanding internists, freely admit making diagnostic errors in these cases, it is easy to see how difficult this and similar differentiation may be at times. However, again, the methodical history and the careful follow-up are usually the deciding factors in an accurate diagnosis.

Cases of renal colic are notably difficult to distinguish from biliary colic, and either may at times cause pain referred more to the mid-epigastrium or lower chest.[14]

An instructive case to me was that of Mrs. N. G. W. who was seized with sudden severe epigastric pain an hour after her breakfast. This pain was constant and involved the lower third of the substernal area with radiation to the shoulders. The pain lasted two hours, was not appreciably relieved by a hypodermic of ¼ grain of morphine but finally vomiting occurred and following emesis there was marked relief. The patient was 57 years of age. Blood pressure at the time of her attack was 150 systolic and 72 diastolic. Examination showed an anxious facies, cool damp skin, pulse 92, regular and good volume. Some dyspnea was apparent. There was moderate but definite tenderness over the upper belly generally, most marked in the epigastrium but without muscle spasm. Examination of the heart showed it to be

normal in size and position but with a roughening of the first sound over the aortic area without significant change in the second sound. My impression recorded at the time was "acute coronary occlusion." The following day she was more comfortable but still complained of chest, epigastric and shoulder pain. The upper abdomen was still sensitive to pressure. Blood pressure 140/70. The following day, 48 hours after the initial attack, she complained again of some increased pain low under the sternum and in the epigastrium. She had felt chilly and her temperature at this time was 100° F. The day following she was more comfortable, her temperature was normal and her blood pressure 100/55. I felt pretty secure in my diagnosis of an occlusion and awaited the time for an electrocardiogram to establish the diagnosis beyond question. This was made and to my surprise and chagrin proved to be entirely normal in every respect. At about this time she again experienced an exacerbation of her acute pain and again had a slight fever. This continued for several days and by this time even I was convinced that her difficulty was not due to a coronary accident. She improved but still had intermittent attacks of pain and some fever. The past history of this case included a cholecystectomy one year before when a gall-bladder containing stones had been removed with an unusually gratifying postoperative recovery. She had experienced a good deal of bladder irritability in the past, otherwise her past history seemed irrelevant. A month had passed by this time since her original acute seizure and during this time her bladder symptoms became more pronounced. Urine examination had been made repeatedly and always showed a trace of albumin and some increase in leukocytes with occasionally clumping but no red blood cells. With the increase in her urinary symptoms attention was directed to a possible pyelitis as responsible for her present illness and with this in mind she was hospitalized and a complete genito-urinary survey done by a competent urologist. He reported a trigonitis and a positive streptococcus culture from the left kidney, and otherwise negative findings. While we were thus struggling, trying to eradicate all urinary tract infection and believing that at last we had found a possible basis for her symptoms, she disappointed all of us again by having an acute episode of severe epigastric pain, with nausea and vomiting. This time, however, tenderness was much more marked in the right hypochondrium. After surgical consultation, laparotomy was decided upon and the following day a stone was removed which had partially obstructed the common bile duct. The obstruction had not been sufficient to produce clinical jaundice. This was a year ago and she has remained entirely free from symptoms since.

This case is an excellent example of diagnostic error committed in the face of low chest and high abdominal pain and was the basis for the present inquiry into the subject.

Acute pancreatitis is always difficult to diagnose. These cases are generally operated upon for intestinal obstruction or acute perforation of an ulcer. This mistake is of no great moment as the diagnosis is quickly corrected when the laparotomy is done. However, operating upon cases of acute coronary thrombosis is bad. Just as bad—probably worse—is failing to operate in the presence of an acute intra-abdominal lesion, believing the symptoms to be coronary in origin. Certain of these mistakes are unavoidable but many need not be made if the cardinal signs and symptoms in each case together with the past history are carefully considered.[15]

Disease of the lungs and pleura may result in low chest or high abdominal pain and may present difficulty in diagnosis. Basal pneumonia in children is often mistaken for intra-abdominal disease. Likewise pleurisy

especially with diaphragmatic involvement at any age.[16] Cases of spontaneous pneumothorax have been reported in which abdominal pain was so great that laparotomy was done.[17] A careful history and careful physical examination should suffice to make a correct diagnosis in most of these instances. There is one type of pulmonary accident, however, that may be very difficult to differentiate and this is sudden pulmonary infarction. These cases may begin with a sudden, terrific pain in the lower chest, or substernal area, and may have radiation of pain into the abdomen, shoulders and arms. The pain is often indistinguishable from that of acute myocardial infarction from a coronary occlusion. However, the dyspnea is usually much more pronounced and often cyanosis is a feature. The differentiation may be made by roentgen-ray examination of the chest and by electrocardiography. However, at the time of the attack the significant factor is in the history of a recent fracture, injury or operation. Postoperative patients rarely have coronary occlusion but not infrequently have pulmonary infarction. Likewise following a fracture a pulmonary infarction may occur.

Such a case was that of Mr. F. C. E., an engineer 49 years of age, who was seen early one morning last November suffering from an attack of severe low chest and substernal pain. This attack had begun during the night. The pain was the most severe the patient had ever experienced and as his history revealed that five years before he had had a gall-bladder removed because of repeated attacks of gall stone colic and that three years before he had passed a stone from his bladder following a severe attack of kidney colic, I thought he must know when he said he had experienced severe pain but that this attack easily topped them all. This pain radiated from his chest to his neck, to his left shoulder, and down the left arm to the wrist. He appeared to be critically ill. His facies was anxious, skin pallid, grayish, and covered with sweat, dyspnea most marked and some cyanosis was noted of the lips and nail beds. His temperature was 97.6°, pulse 100, regular, small volume. Blood pressure 110 systolic and 70 diastolic.

The patient was at this time wearing a cast on his left foot and leg because of a Potts fracture suffered three weeks before. Within the next few hours he suffered two attacks of severe dyspnea and cyanosis but finally pulled out of each. The following day he was somewhat improved but had developed a temperature of 100.2° F. At the end of four days his temperature had returned to normal and he was feeling quite comfortable. An electrocardiogram made two days later was negative and a few days thereafter he was removed to the hospital where a roentgen-ray of the chest showed a small area of opacity in lower lobe of left lung which was interpreted as a resolving infarct in that area. While still in the hospital and exactly two weeks after his initial attack he was again seized with severe pain, dyspnea, and cyanosis; this time, however, the pain was in the lower right chest. Roentgen-ray of the chest at this time showed complete consolidation of the right lower lobe with some free fluid present. The area in the left chest was much decreased. Chest roentgen-ray made at the end of one month showed tenting of the right diaphragm, the result of pleurodiaphragmatic adhesions. The lung fields, however, were entirely clear.

This is an interesting case of pulmonary infarction on the left side occurring three weeks after a Potts fracture, to be followed two weeks later by a second pulmonary infarct, this time on the right side. Hemoptysis is

sometimes present in these large infarcts but was absent in this case. The chief differential point to my mind was the history of Potts fracture three weeks prior, plus a negative history of prior cardiovascular symptoms, such as hypertension or anginal attacks. Final diagnosis depended on a negative electrocardiogram with positive roentgen-ray findings.

To complete our list of possible causes of low chest and high abdominal pain mention must be made of certain affections of the central nervous systems, more especially of the spinal cord or ganglia. I have seen a case of herpes zoster, or shingles, of the lower left chest being treated for coronary thrombosis. This mistake should not be made but the location and severity of the pain were such as to mislead the attending physician. Of course after the typical eruption appeared there was no possible doubt as to the diagnosis. Cord tumors in the low cervical or upper dorsal area may produce severe chest pain. Usually in these cases there is a definite radiation and symmetrical distribution of the pain together with areas of hyperesthesia or anesthesia that are more or less diagnostic. There are, however, cases of bony changes in the vertebrae with spinal irritation which are much more confusing. Here due to irritation of a spinal nerve on one side, there may be severe one-sided chest pain. In 1934 Nachlas [18] described a syndrome of pseudo-angina pectoris originating from demonstrable changes in the cervical spine. The distinguishing feature in these cases is that ordinarily a careful history reveals the nature of the pain as neuralgic and significantly much accentuated by certain movements of the neck, shoulders or arms, and also aggravated by walking or jarring. Often too this pain is definitely confined to the radiation of a specific spinal nerve. The shoulder girdle is primarily involved in most of these cases and a diagnosis at one time or another has been made of arthritis of the shoulder.[19] We have had one case of Paget's disease where chest pain was a prominent feature and here the pain was thought due to bony changes in the cervical vertebrae, with resulting nerve irritation. Mediastinal tumors may by pressure also produce spinal ganglia irritation with the same symptoms.

Even yet our list is far from complete. There are still other causes of low chest and upper abdominal pain—tabetic crises, lead poisoning, uremia, eclampsia, diabetic coma,[20] acute gastritis, mucous colitis, dissecting aortic aneurysm, carcinoma of bronchus and lungs, hyperthyroidism,[22] paroxysmal tachycardia, sensitivity to tobacco, tea or coffee [23] and marked anemia, are some causes mentioned in the literature. There are undoubtedly others. We have tried to limit our discussion to the more usual and the more often confused causes of pain in this area.

In conclusion sudden, severe pain in the lower chest and upper abdomen is a symptom common to many affections of several different systems of the body. Diagnosis in these cases is often difficult because the pain may be the same in all. Accurate differentiation must be based not so much on the pain itself as upon careful consideration in each case of the accompanying history, symptoms and physical signs.

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THE CHEMICAL NATURE OF HEART FAILURE*

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HEART failure in its commonest and simplest form represents an inadequacy in contraction of a critical number of individual heart muscle cells. Every clinician has witnessed the death of patients with evidences of complete myocardial insufficiency only to have pathologists offer nothing more than slight microscopic myocardial changes to account for the clinical picture. In such instances, we have hesitated to admit the histological abnormalities as full explanation of the complete insufficiency in myocardial function. On the other hand we have seen serious and extensive pathological processes demonstrated in the hearts of patients who during life have shown no evidence of primary heart failure. It has, therefore, been widely appreciated that anatomical findings in themselves often fail to show satisfactory correlation with the functional status of an organ.

Unwillingness to accept a purely structural basis for myocardial weakness has initiated research that has been directed toward the establishment of a more adequate concept of the disturbance in fundamental cellular physiology. In comparison with the tremendous amount of physiological data that have accumulated concerning the physical or mechanical response of the heart under various conditions, studies of the disorders of the cellular metabolism or biochemistry of the heart muscle cells have been relatively few and the available data are meagre. Within the last decade, however, considerably more attention has been accorded the chemical physiology of the heart. Derangement of the physicochemical processes concerned in cardiac muscular contraction has long been suspected.

Meakins,[1] in a paper in the ANNALS OF INTERNAL MEDICINE in 1932, directed attention to the newly established facts concerning phosphocreatine (Fiske and Subbarow[2]) or phosphagen (Eggletons[3]) in the skeletal muscle physiology and commented upon a possible analogy in heart muscle function. He, however, stressed the importance of cardiac glycogen and lactic acid formation as affected by oxygen deficiency and acidosis and other metabolic disturbances and related them to circulatory failure.

The important conditions known to lead to failure of the cardiac muscle to function properly, in the light of Meakins' investigations, were similar to those of Harrison[4] and the Vanderbilt group, namely oxygen want, insulin deficiency and a defect in cardiac glycogen metabolism. He discussed other related metabolic disorders as thyrotoxicosis and mentioned the newer concepts of muscle chemistry but confined his main thesis to glycogen

* Read at the St. Louis meeting of the American College of Physicians, April 19, 1937.
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Aided by Grant No. 444 from the Committee on Scientific Research of the A. M. A.

metabolism, which subject he and his co-workers have investigated. Evans [5] and his group, and Cruickshank [6] and his associates, Himwich [7] and others have made further contributions to this phase of the subject.

Eppinger [8] and his school in 1927 demonstrated the increased lactic acid content in the peripheral blood in heart failure and held accountable for this an oxygen want in the skeletal muscles. The demand for oxygen in the periphery, Eppinger et al. concluded, would lead to an increased peripheral blood flow on the arterial side in spite of venous stasis and an increasing oxygen debt and thus would create a vicious circle. Jahn [9] suggested that the persistent flooding of the organism with lactic acid might contribute to the exhaustion of an otherwise damaged heart. Glycogen and lactic acid metabolism maintain a position of importance in heart muscle investigations in spite of the present interest in other substances. The intermediate products of carbohydrate metabolism are closely linked with phosphates; glycogen breakdown appears to yield hexosephosphates and these subsequently may be converted into lactic acid via the formation of various triose phosphates.

Lundsgaard's [10] observations that muscle poisoned with iodoacetic acid could contract without the formation of lactic acid called for modification of the Hill and Meyerhof theory which considered muscle action wholly dependent on glycogen and lactic acid metabolism. The most studied processes in energy liberation in muscle were thus relegated to a secondary position and the fact emphasized that the chemical energy of muscular contraction had to come from another source. Embden [11] and his co-workers had shown that at the end of contraction the reaction was normally alkaline and not acid. Embden had also observed that phosphates played a rôle in muscle cell metabolism.

The American workers, Fiske and Subbarow [2] discovered a labile "phosphocreatine," a K salt or compound of creatine and phosphoric acid, which they considered the primary constituent necessary for muscular contraction. The practically simultaneous independent report of the Eggletons [3] in England of a similar organic phosphate compound which they called "phosphagen," and later recognized to be identical with phosphocreatine, established the latter as the active principle of muscle cells. Both groups of workers found the compound to break down exothermically to supply the energy for muscle contraction.

Halogen acetic acid has been found to stop the anaerobically beating heart by striking at the change from phosphoglyceric to phosphopyruvic acid which is one of the steps in the anaerobic mechanism available for the supply of energy for resynthesis of creatine phosphoric acid. Glycogen is broken down to lactic acid which appears only at the end of contraction and contributes, according to Lehnartz,[12] Embden and Deuticke [13] and Lohmann and Meyerhof,[14, 15] the energy for the resynthesis of phosphocreatine under such circumstances. The combination or the intermediate product lactacidogen or hexosephosphate may act as a buffer.

Analogies between skeletal and cardiac muscle physiology have been drawn and are being gradually established. Clark and the Eggletons [16] early pointed out that the myocardium contains but one-tenth to, at the most, one-fourth, as much phosphocreatine as voluntary muscle. They considered the lower levels adequate in that the diastolic pause following each systole allowed sufficient time for resynthesis, and tetanization cannot occur. Vollmer [17] found phosphocreatine constituting 75 to 80 per cent of the total creatine at rest, but only 20 to 25 per cent at the end of contraction.

Other phosphate compounds as adenylic acid and hexosephosphate were found by Pohle [18] and also by Pollock, Flack, Essex and Bollman [19] to be present and active in heart muscle. In the breaking down of phosphocreatine, the phosphorus liberated is taken up by the adenylic acid to form adenosine triphosphoric acid; this reaction is reversed during the resynthesis of phosphocreatine. During the coincident carbohydrate metabolic cycle, there is an exchange of phosphorus between the hexose and triose phosphates on one hand, and adenylic and adenosine triphosphoric acids on the other. Lohmann has demonstrated adenylpyrophosphate and adenosine diphosphate in heart muscle. Cruickshank [6] states that adenylic acid is only abnormally present in heart muscle when synthesis of adenosine triphosphoric acid is incomplete. Under such conditions he states that the free adenylic acid or adenine would be deaminated to inosinic acid or hypoxanthine and ammonia. Incomplete phosphocreatine formation, a lack of prompt rephosphorylation of creatine, a depletion of glycogen reserves and an increase in orthophosphates, all might accompany progressive heart failure. In anoxic states or in the presence of inadequate oxygen supply theoretically the resynthesis of adenosine triphosphoric acid would lag behind the formation of lactic acid and creatine and ammonia would be formed and lost.

Clark, Eggleton and Eggleton [16] showed that the ratio of phosphocreatine to orthophosphate under favorable normal aerobic conditions was 0.6 for the frog's heart and 1.0 for the tortoise. Cruickshank [6] and his associates demonstrated a similar relationship for the mammalian heart and concluded that the phosphocreatine-orthophosphate ratio is an index of the physiological condition of the mammalian heart.

An index of phosphocreatine, the so-called total creatinine of muscle most of which is creatine, must be established. It is also apparent that, in addition, in order to obtain more complete chemical data in human and animal heart muscle in various functional states the amounts of phosphorus compounds must be determined.

The total phosphorus (Pt), includes a fraction that is soluble in 5 per cent trichloracetic acid and an insoluble fraction. The acid soluble phosphorus (Pas) fraction, according to Lehnartz,[12] is made up of inorganic or orthophosphoric acid (Po), phosphocreatine, hexose phosphate, nucleotid phosphoric or adenylic acid as adenyl pyrophosphoric acid or adenosinetriphosphoric acid, and constitutes the " activity substances " of Embden.[22] The fraction not soluble is the residual phosphorus and consists, according

to Sorg [29] and Wassermeyer [30] of phosphatids or lipids. Cullen, Wilkins, and Harrison [28] found the total phosphorus to be low in the myocardium of a small series of patients who had died in congestive heart failure.

Sorg [29] has shown that the difference between the total phosphorus and the acid soluble phosphorus very closely approximates the lipoid phosphorus (Plip), which is difficult to determine directly. Wassermeyer [30] has found that the total and acid soluble fraction did not change after the death of the muscle and could be studied in human autopsy material and followed a regular distribution in different parts of the dead heart. White,[31] Kutchera-Aichenberger [32] and Lehnartz [12] all considered the lipoid phosphorus important since they found that heart muscle contained twice as much as did skeletal muscle in most animals. Kutchera-Aichenberger [32] found decreases in lipoid phosphorus after experimental myocardial injury produced by chloroform and in human autopsy material from heart failure cases but Wassermeyer and Rohrbach[33] found no lipoid changes in various types of experimentally induced myocardial damage.

According to Wassermeyer [30] human hearts show a regular decrease in these substances, particularly the lipoids, as the age advances toward 70 years. Coronary sclerosis in hearts was accompanied by a regular decrease in the total phosphates but also a drop in the lipoids. In a few decompensated hearts, there were no significant changes in the total phosphate but usually a definite lowering of the lipoids in the left ventricle.

The possible importance of this lipoid fraction was further emphasized by theoretical considerations of the physicochemical possibilities, namely, the probable importance of lipoid phosphates in the processes at the cell surfaces. The susceptibility of the lipoid phosphates to changes brought about by calcium and indirectly by digitalis administration increases the desirability for further investigation of these substances.

A Biochemical Approach to the Problem of Human Heart Failure

We have, during the past ten years, directed studies in the fundamental chemical changes that accompany heart failure. At first, we were concerned with the part played by inorganic salts of calcium and potassium.[20, 21] With the gradual development and diffusion of the newer conceptions of phosphocreatine or phosphagen in muscle physiology, we began our investigations of the organic constituents of the heart muscle. We have analyzed the heart muscle of animals under various experimental conditions and of human autopsy material. Determinations of the total creatinine (practically all of which is creatine), of total and acid soluble phosphorus as well as of calcium and potassium were made.

The great technical difficulties in determining phosphocreatine in mammalian muscle and the impossibility of determining phosphocreatine in human heart muscle halted for some time progress in the matter of clinicopathological biochemical studies. The suggestion of Pekelharing [22] carried

out by Constabel [23] and by Seecof, Linegar and Myers [24] and by Cowan [25] on the relation of the creatine content of human heart muscle to myocardial function gave great impetus to further research along this line. The acceptance of the total creatinine content of dead heart muscle as a probable index of the level of phosphocreatine in life afforded a means of attack of the problem. Instead of the labile phosphocreatine, we have, therefore, determined the total creatinine in our experimental and clinical material.

In the beginning, we undertook studies of blood and urine constituents, particularly total creatinine and creatine, in patients with acute coronary obstruction and myocardial infarction.[26, 27] We found a definitely abnormal creatinuria and a rise in the blood creatine levels beginning within a few hours after the onset of an attack and continuing for several days to a week depending perhaps upon the size of the infarct.

Experimental Total Creatinine Studies

A series of dogs was sacrificed at varying periods of time after the occlusion of the blood supply to a section of the myocardium by tying of the anterior descending branch of the left coronary artery. We substantiated the finding of a sharp drop within the first few hours in the glycogen content of muscle from the infarcted areas. We also noted slightly delayed but striking loss of total creatinine, beginning after the fifth hour of infarction.[27]

The problem was then attacked further experimentally in various ways and chemical analyses of the heart muscle were carried out after the production of various types of experimental myocardial damage.

Another series [24] of rabbit hearts was isolated and perfused for six to eight hours in a modified Dawson-Gunn-Locke apparatus with warm oxygenated Ringer-Locke solution. The hearts in this series that were infarcted, by the lodgement in their coronary arteries of small particles from the perfusion fluid, showed the lowest total myocardial creatine values that we encountered. The uninfarcted hearts that were perfused to failure, which occurred at the end of six to eight hours, likewise presented very low creatine content. It was further shown that a fall in the pH due to lactic acid accumulation in the perfusate was accompanied by an added loss of creatine.

Further experimental attempts [32] to stay the dissipation of total creatinine were carried out. Some of the various amino acids that have been suggested as possible precursors of creatine, namely glycocoll, glycocyamine, arginine, alanine, glutamic acid, aspartic acid, methylguanidine, and creatine itself were added to the perfusate and the effects were noted. In our studies all amino acids with the possible exception of alanine and to a slight extent glycocoll, failed to maintain normal total creatinine values in the isolated heart. Alanine seemed to spare the creatine, and its effects as that of glycocoll, might be attributed to its protein stimulating properties as suggested by Professor B. M. Hendricks. That these amino acids are utilizable by the

heart for the production of energy seems possible from our results.[6] However, we could not demonstrate any definite building up of creatine. Fisher and Wilhelmi,[36] Davenport, Fisher and Wilhelmi [37] have recently challenged this conclusion.

Experimental myocardial destruction was produced in a large series of rabbits by injection intravenously of caffeine sodium benzoate and adrenalin and similar striking losses of total creatinine were demonstrated in the damaged heart muscle.[38]

In another series of rabbits that we studied with E. H. Schwab [39] we produced aortic insufficiency and the resulting hypertrophied hearts were carefully weighed and analyzed. Half of these animals were digitalized and the other half were not. A series of normal animals and a series of uninjured digitalized animals were simultaneously sacrificed and the heart muscle analyzed. The hypertrophy in the very earliest cases was found to be associated with a relative increase as well as an absolute increase in total creatinine. When hypertrophy became definite and conspicuous as revealed by such gross tests as the heart weight/body weight (H.W./B.W.) ratio, the total creatinine percentage was about normal. In some there was a relative percentage drop in total creatinine; however, the total quantity of creatinine, taking into account the greatly increased weight of the heart, was uniformly definitely elevated. Digitalization usually prevented the percentage drop and thus contributed to distinctly higher total creatinine values. Digitalization showed similar effects upon normal and uninjured hearts in that there was a definite retention or augmentation of the normal total creatinine values.

Human Heart Total Creatinine Studies

In view of the probable significance of the physiological and pathological chemical changes in heart failure, we considered it worth while to continue the clinical as well as the experimental investigation of this interesting albeit difficult subject. We undertook to determine the chemical end results as they appeared in hearts from human autopsy material as well as in the animal hearts. The studies of total creatinine previously reported in groups [40, 41] have been confirmed by the addition of a great many more specimens and analyses.

In our series of over 500 adult human hearts * to date there have been 374 hearts from patients who died without showing definite evidence of congestive heart failure and 127 from patients who died in congestive heart failure. The hearts from the 374 patients who had not presented evidence of myocardial insufficiency showed average total creatinine levels of 175.3 (±) 12.5 mg. per cent (standard deviation). In contrast the 127 hearts

* We are indebted to Prof. Paul Brindley of the Department of Pathology and his staff, particularly Dr. Tom Oliver, Dr. Sion Holley, Dr. M. P. Kelsey, Dr. Jarrett E. Williams, Dr. John S. Shaver, Dr. James Chambers and Gene Thieme. The chemical analyses were made by Peter Erhard.

that had failed contained an average of 125.5 (±) 25.4 mg. per cent (standard deviation) of total creatinine.

Statistical studies of these data, considering the variations that are presented in this series by applying the "t" test of Fisher, proved the differences to be significant with a P value of less than .01, so that the probability of obtaining such differences by pure chance is practically nil. The low total creatinine values are, therefore, very significant findings in the hearts of patients dead of congestive failure in spite of occasional inex-

TABLE I

Total Creatinine Content of Hearts from Patients Dead of Various Conditions

Cause of Death	No.	Solids %	Wet Creatine	Dry Creatine	Potassium
Surgery, trauma, tumors.	66	20.42±0.12 S.D. 1.42	176.7±1.52 S.D. 18.2	871 ±13.6 S.D. 164.2	255.5±4.7 S.D. 43.7
Hypertension, cerebral hemorrhage.	33	20.72±0.16 S.D. 1.4	196.0± 3.8 S.D. 32.7	950 ±17.1 S.D. 146.7	277 ± 6.3 S.D. 47.0
Congenital cardiovascular disease. Associated rheumatic, without congestive failure.	15	20.74±0.26 S.D. 1.5	161.0± 7.8 S.D. 45	771 ±31.7 S.D. 182.6	268.1 S.D.
Syphilitic cardiovascular disease without congestive failure.	25	20.85±0.21 S.D. 1.54	160.0± 1.6 S.D. 37.1	766 ±19.6 S.D. 146	247 ± 9.0 S.D. 53.7
Infectious disease; bronchopneumonia. Pericarditis, endocarditis.	120	20.63±0.08 S.D. 1.25	182.0± 2.1 S.D. 33.7	888 ± 9.8 S.D. 160.8	255 ± 3.5 S.D. 45.1
Lobar pneumonia.	24	20.24±0.23 S.D. 1.70	150.0± 5.7 S.D. 36	777 ±26.2 S.D. 191	251 ± 9.5 S.D. 60
Tuberculosis.	27	19.50±0.17 S.D. 1.30	163.0± 4.1 S.D. 31.7	822 ±18.8 S.D. 145	248 ± 7.6 S.D. 48.9
Uremia.	20	21.18±0.21 S.D. 1.4	171.5± 4.2 S.D. 28	809.6±17.6 S.D. 117	252.6±12.7 S.D. 59.6
Chronic glomerulo-nephritis.	6	20.42	161	791	
Hepatic cirrhosis.	8	20.58	178	919	256
Acute myocardial degeneration.	35	20.09±0.14 S.D. 1.26	155.5± 3.1 *S.D. 27.8	767 ±15.6 *S.D. 139.6	240 ± 6.9 S.D. 53.1
Anemia; massive hemorrhage.	79	20.18±0.11 S.D. 1.46	153 ± 2.4 *S.D. 32.	769.7±12.5 *S.D. 164.2	236.3± 4.8 S.D. 50.2
Asphyxia.	22	20.00± .20 S.D. 1.42	134.9± 2.9 *S.D. 21.2	674.7±16.5 *S.D. 114.8	228 ± 9.6 S.D. 55
Coronary obstruction.	33	20.27± .12 S.D. 1.05	125 ± 3.0 *S.D. 25.5	605 ±17. *S.D. 145.6	240 ± 2.8 S.D. 44
Congestive failure.	127	20.04± .01 S.D. 1.3	122.5± 1.5 *S.D. 25.4	611 ± 8.1 *S.D. 135.3	240 ± 2.8 S.D. 40

*Statistically significant variation from normal.

TABLE II

Creatine Content of Hearts from Patients Dead of Coronary Obstruction

Averages 33 Cases Left Ventricle Tot.	Solids 20.27%	Wet Creatine 125.0	Dry Creatine 605	Potassium 240
Infarcted areas Uninfarcted areas	20.20%	85.0 145.0	420 730	217
Infarcted areas Uninfarcted areas	17.25% 19.15%	79.0 151.0	387 735	175
Infarcted areas Uninfarcted areas	18.80%	78.0 152.0	414 812	264
Infarcted areas Uninfarcted areas	20.05%	76.0 132.0	380 657	230
Infarcted areas Uninfarcted areas	20.90%	74.0 138.0	354 660	268
Infarcted areas Uninfarcted areas	18.05% 21.95%	61.4 105.0	340 480	147
Infarcted areas Uninfarcted areas	18.20% 19.70%	58.5 110.5	321 560	165
Infarcted areas Uninfarcted areas	18.20% 19.70%	52.0 100.0	318 558	
Infarcted areas Uninfarcted areas	19.44% 20.94%	58.0 78.0	277 402	
Infarcted areas Uninfarcted areas	20.45% 22.75%	42.0 122.0	205 538	246.5
Infarcted areas Uninfarcted areas	17.25% 19.15%	31.0 151.0	180 788	

plicable high and low levels. Possible effects of other conditions, particularly those that interfere with oxygenation of the heart, on the creatine levels may be noted in a careful perusal of tables 1 and 2.

Along with our experimental and clinical studies, we have reported corroborative studies of the total creatinine content of hearts from patients

TABLE III

Phosphorus Values in Human Heart Muscle

Cause of Death	Number of cases	mg. % P. tot.	mg. % Pas.	mg. % Plip.	mg. % Po.
Other than congestive failure	384	189 −3.92	90.1 −2.2	90.9 −4.08	43.9
Congestive failure	127	162 −6.8	72.4 −1.3	89.5 −1.39	41.8

P. tot. = total phosphorus; Pas. = acid soluble phosphorus; Plip = lipoid residual phosphorus; Po. = inorganic or other phosphorus.

who had died of coronary thrombosis and cardiac infarction [10] as shown in table 2. Upon analysis the total creatinine content of the infarcted areas of human hearts was far below the concentration of the total creatinine in the uninfarcted myocardium, though this latter was also definitely reduced from normal.

Human Heart Phosphorus Studies

Inasmuch as the total phosphorus and the acid soluble phosphorus may be determined with a fair degree of accuracy and the difference between the two represents very closely the figures obtained directly for the lipoid phosphorus, we have extended our chemical analytical procedures to include total phosphorus, acid-soluble phosphorus, lipoid phosphorus, ortho or inorganic phosphorus, and potassium. These fractions with the exception of the labile components of the acid-soluble portion, are considered to be stable and not subject to change for 24 to 48 hours after death. The Pas according to Embden contains the individual "activity substances" in the heart muscle.

The inorganic or orthophosphorus values shown in table 3 in heart muscle of patients dead of heart failure and of other conditions did not differ significantly. We found as Wilkins and Cullen [27] had that the total phosphorus values were lowered statistically significantly in the hearts of patients dead of congestive failure.

In our earlier group of cases, the lipoid phosphorus, which we determined by difference, seemed significantly lowered in hearts that had failed. Recent adoption of improved analytical procedures, which obviate any absorption by the abrasive of the acid-soluble phosphorus compounds, reveals [42] that the decrease in total phosphorus in the myocardium that has functionally failed is due to a loss of the acid-soluble components: the drop in the average value for the lipoid phosphorus is too small to be of statistical significance.

We are unable to attribute any significance, when statistical criteria are applied, to the variations from normal of average values for the potassium content in the different groups.

Comments

The tabulation of data of hearts from patients who had died without clinical evidences of congestive failure according to the presence of other striking pathological processes was worth while. It is apparent that other conditions which we recognized clinically as possibly contributory to heart failure may play a rôle in changing the creatine and phosphorus content of the heart muscle. In hearts from patients who presented striking anemia, conspicuous asphyxia as a result of strangling, acute or chronic pulmonary disease, syphilitic aortitis, or coronary artery disease, there were definite subnormal myocardial total creatinine values. The hearts of those with infectious diseases, rheumatic valvular disease, and hypertension with cere-

bral hemorrhage showed fairly normal to elevated creatine values. The lowered total creatinine in pneumonia heart is interesting and may be proved to be significant. The apparent tendency of digitalis to cause an elevation of total creatinine is significant of a chemical myocardial action.

The total phosphorus and acid soluble phosphorus fractions were decreased in hearts that had failed; the small number of cases in the other groups make the variations of doubtful significance.

In the light of these chemical findings, it seems suggestive at least that total creatinine and creatine, total phosphorus and acid soluble phosphorus losses usually accompany heart failure. Whether the chemical changes are the cause of the heart failure or the result of the heart failure is a question that should be raised and as yet cannot be answered. Further experimental evidence is needed. We must substantiate our contention that the losses of total creatinine and phosphates are the factors that lead to myocardial weakness.

It has been generally accepted that in anoxemia, in asphyxia and in aglycemia there is a failure of resynthesis of creatine phosphate. These same conditions, we concluded, might lead to creatine and phosphorus losses from human hearts and ultimate cardiac weakness.[40, 41] Consideration of such facts and our findings lead us to extend Harrison's [4] physical theory of the anoxemic etiology of circulatory failure to include inevitable biochemical changes in heart muscle to account for myocardial insufficiency.

Conclusion

The chemical theory of the mechanism of heart failure has much evidence in its favor.

Even though the theory seems substantiated and the indications simple yet there is, thus far, little that may be done about it.

The perfusion and feeding experiments with the precursors of creatine phosphoric acid have not yet been successful in causing it to build up.

The correction of chronic conditions that lead to anoxemia are in order so far as it is possible to prevent the further dissipation of the essential activity substances.

Oxygen therapy is in order but still is rather impractical. It is so often impossible to get the O_2 to the cells where it is needed.

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MACROCYTIC ANEMIA, OTHER THAN PERNICIOUS ANEMIA, ASSOCIATED WITH LESIONS OF THE GASTROINTESTINAL TRACT *

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A macrocytic anemia may be defined as an anemia in which there is an increase in the number of red blood cells of the circulating blood having a diameter greater than 7.5 microns, and a mean corpuscular volume which exceeds 96 cubic microns. In such an anemia the color index usually is one or higher. It is generally considered to be due to defective blood formation and is frequently controlled by anti-pernicious anemia medication but is not ordinarily benefited by iron therapy.

An anemia of this type is characteristically found in true Addisonian pernicious anemia, in the so-called "tropical anemia" and some cases of sprue, in myxedema, occasionally in leukemia, and for a short interval immediately following an acute hemorrhage. Finally, such an anemia may be the result of a dietary deficiency or various gastrointestinal disturbances.

It is with these latter two causes that this study is primarily concerned. It is not the purpose of this paper to attempt to give an extensive review of the literature concerning the relation of the gastrointestinal tract to the macrocytic anemias. During the past decade, largely through the work of Castle and his coworkers,[1, 2, 3, 4] Meulengracht,[5-9] Goldhamer [10-14] and others,[15-20,22] our knowledge concerning the relation of the gastrointestinal tract to pernicious anemia and other macrocytic anemias has been classified and the apparent diverse causes for such an anemia have been correlated and an understanding concerning their inter-relationship has now been reached.

In order to understand these, it is necessary to review briefly the normal process by which the red blood cells are developed and released to the peripheral blood. This is accomplished, according to Castle,[1, 2, 3, 4] as follows: Some unidentified substance which is called the "extrinsic factor" is ingested in the diet and this reacts with an "intrinsic factor," probably an enzyme, which is contained in the gastric secretions. As a result of this reaction, a substance is formed which controls the rate of formation of red blood cells in the bone marrow. Since the red blood cells are not normally released until they are mature, any disturbance in the formation of the substance controlling the maturation of the erythrocytes, will diminish the number which are released to the peripheral blood and an anemia will develop. It has been demonstrated by Castle that pernicious anemia is due to

* Delivered before the American College of Physicians, New York City, April 7, 1938.
From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

a gastric defect which results in absence of, or, as Goldhamer [10,11] has shown, a diminution of the intrinsic factor, while the macrocytic anemia which may be present in sprue is thought to be due in some cases to a lack of the extrinsic factor.[21] Even though the intrinsic and extrinsic factor reaction occurs in an individual, other conditions may prevail which prevent the erythrocyte maturing substance from performing its normal function. For example, there may be a failure to absorb the material which results from the interaction between the extrinsic and intrinsic factors, as a result of intestinal anastomoses or stricture.[5] Furthermore, it is now generally accepted that extensive liver disease [13, 14, 20] which prevents the storage of the erythrocyte maturing substance, may cause a macrocytic anemia.

The gastrointestinal lesions which may be associated with a macrocytic anemia may be stated briefly as follows: Total gastrectomy, extensive infiltrative carcinoma of the stomach, various lesions of the intestines such as stricture and anastomoses, and extensive liver disease which may be the result of widespread cirrhosis or some other process such as an acute hepatitis.

These blood changes are important for several reasons. From a practical standpoint macrocytic anemias are of significance because of the therapeutic indications. They yield, in many instances, to anti-pernicious anemia medication, especially to the parenteral administration of liver extract. On the other hand, iron, while it may be of value in rare instances, ordinarily is of no benefit. From a theoretical point of view, the various gastrointestinal lesions which cause such an anemia are of the greatest interest, not only from the standpoint of etiology but also because they make clear the mechanism by which the formation of red blood cells is normally controlled.

For the past 11 years it has been our privilege to observe a large group of patients with pernicious anemia at the Simpson Memorial Institute. During the course of our studies a number of patients with macrocytic anemia have been observed who have illustrated very strikingly the various types of gastrointestinal lesions which may cause such an alteration in the blood.

The following are the case histories of the patients on whom these observations were made.

Case Reports

Case 1. V. M., female, aged 27, was admitted May 21, 1929 with chief complaints of vomiting, weakness and cramp-like pain in the stomach. She reported that for about a year she had had "gastric upsets" characterized by nausea, vomiting and severe cramp-like abdominal pain. These symptoms gradually increased in intensity and for a few weeks before admission she had been unable to retain even fluids. There had been a 20 pound weight loss during the present illness. A few weeks before admission she had been troubled with dyspnea, palpitation, dizziness and headache.

Physical examination showed an emaciated, under-nourished female with mild pallor. There was a soft tender mass above and to the left of the umbilicus. The

red blood cell count was 4.27 million per cu. mm., hemoglobin 70 per cent. Gastric analysis after injection of histamine showed no free hydrochloric acid. The Kahn reaction was four plus. Roentgen-ray examination showed an irregularity at the prepyloric region of the stomach and on the greater curvature, with complete obstruction. The most probable diagnosis was hereditary lues and the patient was treated with antiluetic therapy for a short interval. On account of the vomiting and inability to retain fluids, however, it was thought an operation should be performed without further delay and the lower half of the stomach was resected and a gastrojejunostomy was done. About three years later she again had complaints of eructation of gas, nausea and vomiting. Her appetite had been poor and there had been a 12 pound weight loss. Physical examination showed an emaciated female with very marked pallor. The sclerae were icteric. The red blood cell count was 1.18 million per cu. mm., hemoglobin 23 per cent. Gastric analysis following injection of histamine showed no free hydrochloric acid. The patient was treated with oral and parenteral liver extract which caused a characteristic reticulocyte response with a rapid increase of the red blood cells and hemoglobin to normal. The patient has not been seen since leaving the hospital but a letter from her in October 1935 states that she felt perfectly well. After her discharge from the hospital she had eaten some liver every week but had had no other form of therapy. The reaction of the blood to treatment is shown in chart 1.

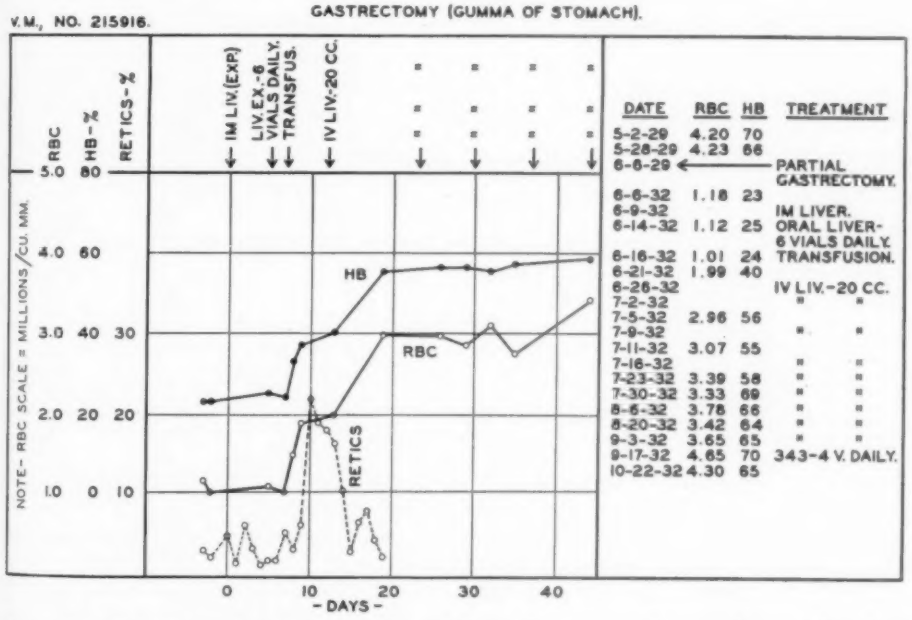

CHART 1. The effect of oral and parenteral liver therapy on the anemia resulting from gastrectomy.

Case 2. A. F., a male, 38 years of age, was admitted to the hospital November 24, 1933, with the chief complaint of pain over the heart.

Present Illness: For four or five months the patient had suffered from vague precordial and epigastric pain which was dull and aching in character. This was brought on by eating, and usually persisted throughout the day. There had been some distress and belching of gas, and also a decrease of 12 pounds in body weight during the present illness.

Physical examination showed nothing of importance except evidence of weight loss. The red blood cell count was not done but the hemoglobin was found to be 92 per cent. Fasting gastric analysis showed no free hydrochloric acid. Roentgen-ray examination disclosed a neoplasm of the posterior wall of the stomach occupying the middle and lower thirds of this organ. Partial gastrectomy and gastrojejunostomy were done on November 7, 1933, at which time approximately two-thirds of the stomach was removed. The pathologic report was medullary carcinoma of the stomach. On April 10, 1936, about three years after the operation, the patient was admitted for a second time complaining of increasing fatigue, weakness, dyspnea and palpitation on exertion. There had been some edema of the lower extremities. Physical examination showed nothing of importance except pallor and pitting edema of the ankles. His red blood cell count was 1.79 million per cu. mm., hemoglobin 40 per cent. The patient was given intramuscular liver extract (Parke, Davis and Co.)

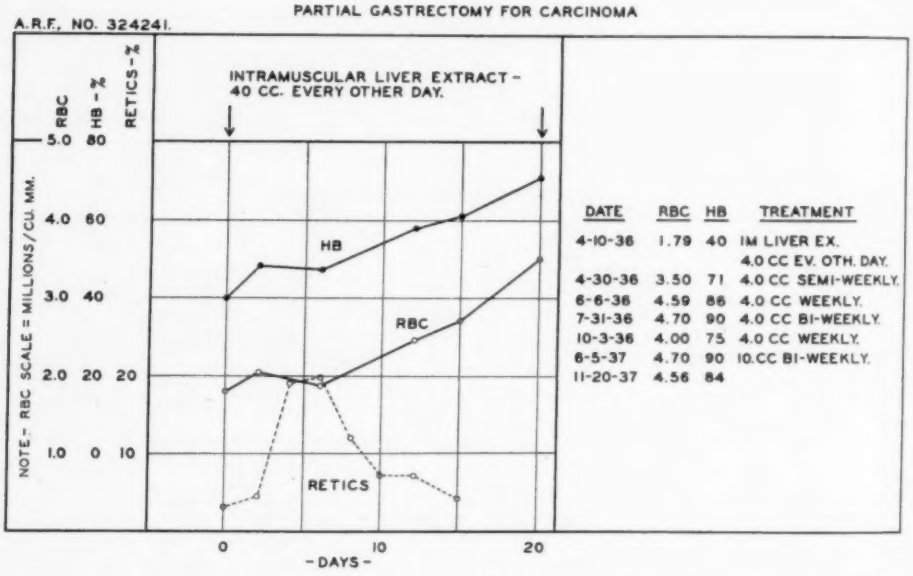

CHART 2. The effect of parenteral liver extract on the macrocytic anemia occurring after gastrectomy.

4 c.c. every other day, which resulted in a reticulocyte rise which reached a peak of 20 per cent. The changes in the blood are shown in chart 2.

Case 3. J. K., a male, 53 years of age, was admitted July 28, 1929 with the chief complaint of a discharging sinus of the chest.

Present Illness: In October 1928 he stated that he developed pleurisy with effusion and purulent fluid was said to have been aspirated on three occasions from the pleural cavity. At this time a microcytic anemia was present which was attributed to infection. He entered the University Hospital and was treated by irrigation and drainage of the empyema cavity. Early in 1930, a thoracoplasty was done, at which time there was a marked increase in the anemia. Following iron medication, however, his blood returned almost to normal. In 1932 he returned to the hospital stating that for four weeks he had suffered with epigastric pain, marked constipation and nausea and vomiting. Roentgen-ray examination showed a polypoid neoplastic mass in the upper two-thirds of the stomach. His red blood cell count was found to be 3.00 million per cu. mm. and hemoglobin 30 per cent.

Gastric resection was performed and approximately two-thirds of the stomach was removed. Prior to the operation the patient had a blood transfusion and was given iron medication for a considerable period of time. For a period of approximately a year, however, he had no anti-anemic therapy and about the middle of 1934 he returned to the hospital, at which time he had a definite macrocytic anemia with a red blood cell count of 2.80 million per cu. mm. and hemoglobin 80 per cent. He was then given intramuscular liver extract and as a result his red blood cell count and hemoglobin became practically normal after three months. He then practically discontinued therapy and when seen early in 1937 he again had a macrocytic anemia with a hemoglobin of 58 per cent and red blood cell count of 2.6 million per cu. mm.

In summary then, the patient first had a microcytic anemia as a result of in-

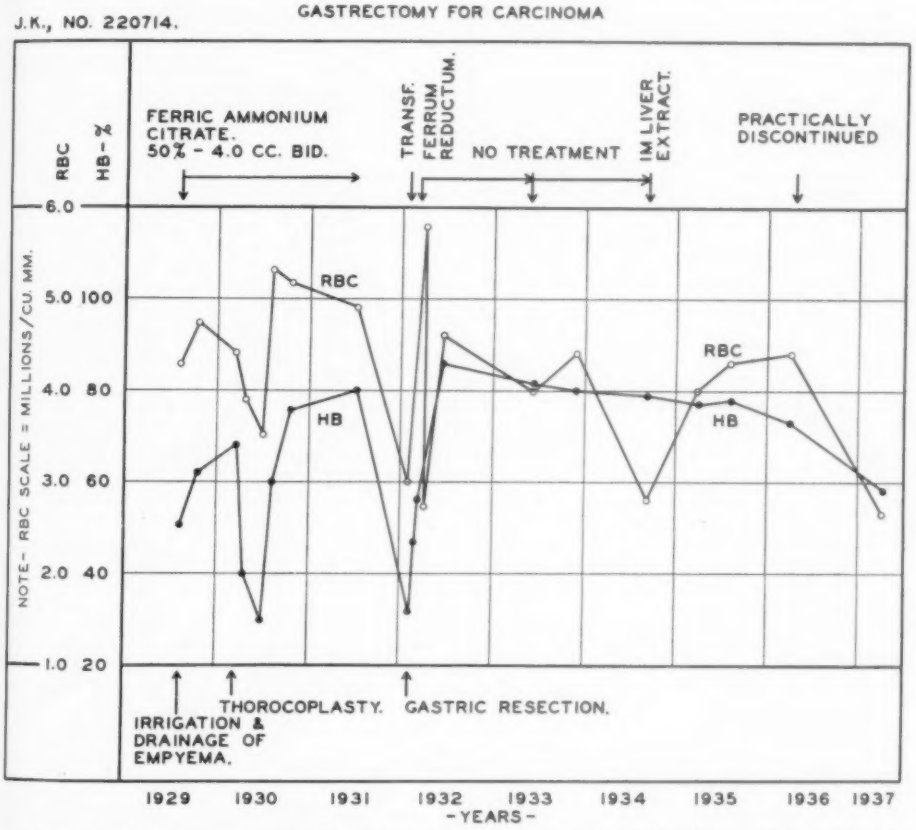

CHART 3. The occurrence of a microcytic anemia associated with infection and carcinoma of the stomach and the subsequent development of a macrocytic anemia, following gastrectomy, which was controlled with intramuscular liver extract.

fection, which disappeared when this was controlled, and following the administration of iron. Some time later he again developed a microcytic anemia which was associated with a neoplasm of the stomach. Following gastric resection, he was found to have a macrocytic type of anemia which was controlled by liver extract for a time, but recurred when the liver extract medication was stopped by the patient. The changes in the blood are shown in chart 3.

Case 4. J. G. K., a male, 63 years of age, was admitted January 30, 1934, with the chief complaints of fatigability, weakness, dyspnea and palpitation.

Present Illness: The onset was four months previously when the patient noted greatly increased weakness and ease of fatigue. This progressed and two months prior to admission he developed dyspnea and palpitation on exertion. Pallor was noted and icterus had been present for three weeks. There had been some distress following meals for a month and a five pound weight loss.

The family history is of interest because his father died of pernicious anemia and the mother and one sister had cancer.

Physical examination showed an elderly male who appeared to be critically ill. The skin was pale and icteric. There was some atrophy of the tip of the tongue and along the margins but it was not the characteristic tongue seen in pernicious anemia. Neurological examination was negative. Gastric analysis showed no free hydrochloric acid. The icterus index was 40, the blood bilirubin was 1.6 mg. per 100 c.c., the red blood cells 1.30 million per cu. mm., hemoglobin 32 per cent (Sahli).

This patient's gastric juice was obtained and after incubation with hamburg steak, according to the technic of Castle, it was administered to another patient with pernicious anemia in relapse, and no reticulocyte response was observed, which indicated an absence of the intrinsic factor.

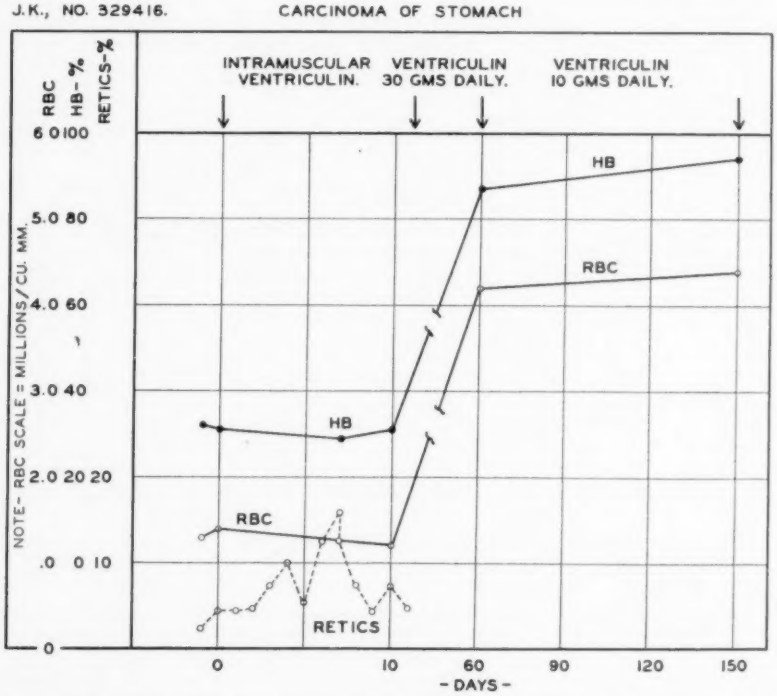

CHART 4. The effect of desiccated stomach on the macrocytic anemia due to *linitis plastica*.

The patient was given an intramuscular injection of an experimental preparation of Ventriculin which possibly was of weak potency. This was followed by a reticulocyte response of 16 per cent on the seventh day of treatment. The patient was discharged from the hospital with instructions to take 30 grams of Ventriculin daily. He returned on April 30, 1934, three months after leaving the hospital, at which time his red blood cell count was found to be 4.22 million per cu. mm., hemoglobin 87 per cent. He returned again on July 31, 1934, stating that for the past month he had had

distress after meals and some nausea and vomiting. His red blood cell count was then 4.38 million per cu. mm., hemoglobin 94 per cent. There had been a 25 pound weight loss during the preceding two months. Roentgen-ray examination at this time showed evidence of *linitis plastica*. Although it cannot be proved, it is assumed that the patient had *linitis plastica* on the first admission and this extensive infiltrating malignant growth had destroyed the gastric glands and as a result there was a lack of the intrinsic factor in the gastric juice. The changes in the blood are shown in chart 4.

Case 5. M. R. N., a female, 46 years of age, was admitted to the hospital on August 10, 1932, with the chief complaints of "weakness and lack of endurance." In 1927 she had three abdominal operations, the first for adhesions causing acute obstruction; at the second, a few months later, four feet of intestines were removed and an anastomosis was done; and at the third operation an anastomosis of the ileum

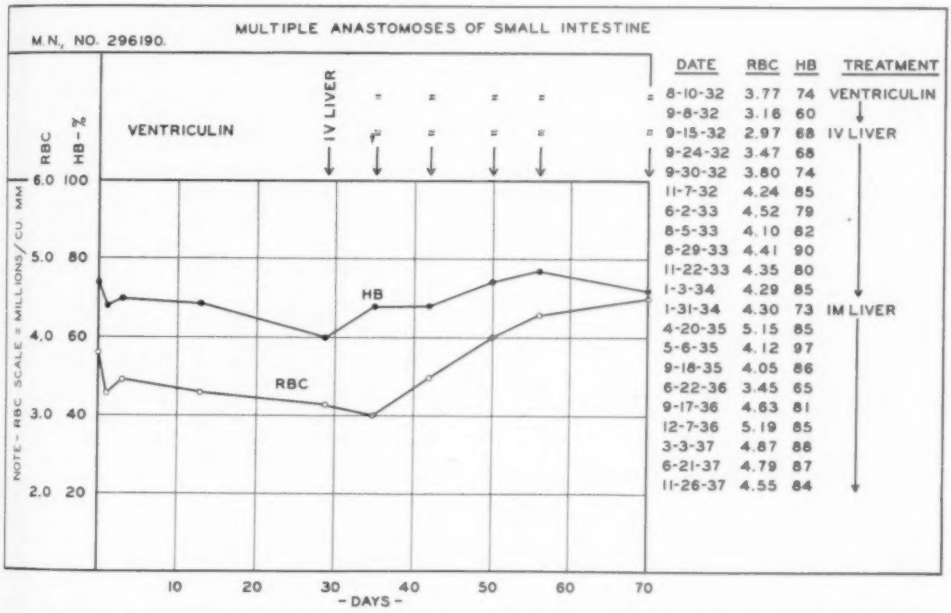

CHART 5. The failure of response to desiccated hog stomach and subsequent elimination by parenteral therapy of the macrocytic anemia associated with multiple anastomoses of the small intestines.

to the ascending colon was performed. The patient remained in good health except for attacks of diarrhea until six or eight months previous to admission, at which time she had influenza which was followed by a prolonged convalescence. At this time she was told her red blood cell count was 2.00 million per cu. mm. She suffered from considerable gaseous distention and had frequent attacks of diarrhea. Occasionally she had rather severe cramp-like abdominal pain. There had been a loss of eight to ten pounds in body weight in the past six months.

Physical Examination: Negative except for evidence of weight loss and a barely palpable liver and spleen. Her red blood cell count was 3.30 million per cu. mm., hemoglobin 70 per cent. Gastric analysis following injection of histamine showed the presence of free hydrochloric acid. The patient was given Ventriculin, 40 grams daily, orally, but the red blood cell count and hemoglobin diminished slightly over a period of 30 days. She then received intravenous liver extract which resulted in a

prompt rise in the red blood cells and hemoglobin to normal. After receiving this form of therapy for approximately two years she was given intramuscular liver extract which maintained her blood at a normal level except for intervals when she grew lax in her treatment. When last seen on November 26, 1937, her red blood cell count was 4.55 million per cu. mm. and hemoglobin 84 per cent. Changes in the blood following treatment are shown in chart 5.

Case 6. C. H., a male, 31 years of age, was admitted on September 27, 1935, with the chief complaint of "abdominal pain." He stated that he had suffered from constant generalized abdominal pain for 12 years, which was not related to meals. Other complaints were belching, flatulence, and intermittent diarrhea and constipation. There had been some nausea and vomiting. No change had been noted in the appearance of the stools. He had noticed a transient swelling in the right lower quadrant accompanied by a gurgling sensation in this area at intervals. There had been a marked weight loss. The patient had an appendectomy in 1923 and in June 1935 an abdominal operation for relief of adhesions.

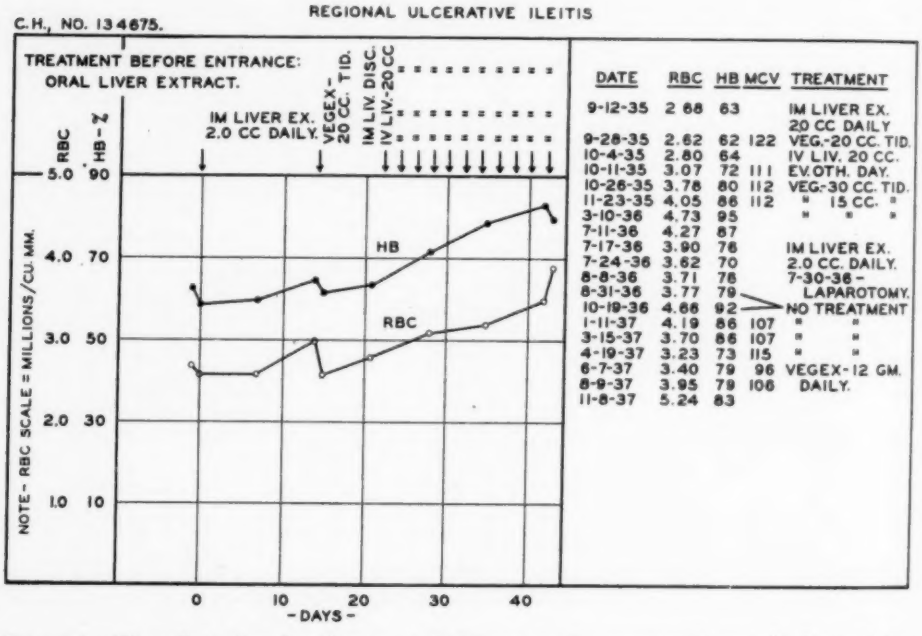

CHART 6. The effect of oral and parenteral therapy on the macrocytic anemia due to intestinal obstruction and spontaneous remission following removal of the intestinal lesion.

Physical Examination: The patient was a poorly nourished, emaciated male, showing some pallor. The tongue was smooth, and showed definite atrophy of the papillae which resembled the change observed in patients with pernicious anemia. There was tympany and distention of the abdomen, and tenderness in the right lower quadrant. The neurological examination was negative. On his first admission the red blood cell count was 2.19 million per cu. mm., hemoglobin 65 per cent. Fifty-eight per cent of the cells were larger than 7.5 microns and the mean corpuscular volume was 122 cu. microns. Gastric analysis following administration of histamine showed the presence of free hydrochloric acid. Roentgen-ray examination indicated that there was a delayed emptying of the small intestine. He was treated with intramuscular liver extract (Parke, Davis & Co.) 2 c.c. daily and following this

there was a reticulocyte rise to a peak of 5.8 per cent. In addition he was given Vegex, 20 c.c. three times daily. Later 20 c.c. of liver extract (amount derived from 100 grams of liver) were given daily for 11 days. With this his red blood cell count rose promptly to 3.90 million per cu. mm. and hemoglobin to 80 per cent. The patient was then treated with variable amounts of Vegex. The patient was re-admitted on July 13, 1936, with a recurrence of all abdominal symptoms. On this admission the red blood cell count was 4.20 million per cu. mm. and hemoglobin 87 per cent. On July 30, 1936 a laparotomy was performed and 2½ feet of lower ileum were resected. The pathological report was regional ileitis. The patient was discharged without further treatment. On October 19, 1936, the red blood cell count was 4.60 million per cu. mm., hemoglobin 92 per cent. He had a recurrence of his symptoms and returned on April 19, 1937 with a red blood cell count of 3.25 million per cu. mm., hemoglobin 73 per cent. The mean corpuscular volume was then 115 cu. microns. He was again treated with Vegex and when last seen on November 8, 1937, the red blood cell count was 5.24 million per cu. mm., hemoglobin 83 per cent. He still complained of abdominal cramps. The changes in the blood are shown in chart 6.

Case 7. M. P., a female 52 years of age, was admitted December 10, 1936, with chief complaint of "diarrhea."

Present Illness: Patient stated that during the past year she had had 10 to 12 watery stools daily. She had not noticed that they contained blood or mucus. Occasionally she had had nausea and vomiting, and there had been a weight loss of 40 pounds in the last ten months. She had had frequent attacks of glossitis. During this time the patient had been on an adequate diet.

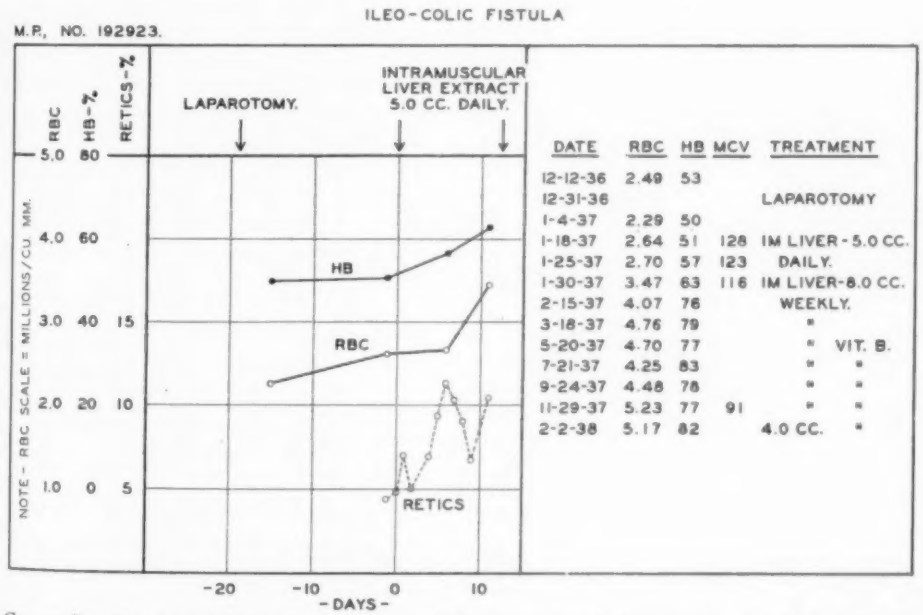

CHART 7. The hematologic response to effective parenteral therapy in a patient with an ileocolic fistula.

Physical examination showed an emaciated, pale female. The tongue was clean and appeared to be normal. The abdominal examination was negative. There was slight edema of the ankles. The red blood cell count was 2.49 million per cu. mm. and the hemoglobin was 53 per cent. Fifty-three per cent of the cells were larger

than normal. The gastric analysis showed free hydrochloric acid. Roentgen-ray examination of the gastrointestinal tract disclosed an ileocecal fistula. The patient was operated upon December 31, 1936 and an unsuccessful attempt was made to repair this condition. It was thought that the patient had had an old tuberculous salpingitis with a localized peritonitis which accounted for the condition, but biopsy showed nothing but chronic infection. The patient was placed on intramuscular liver extract, 5 c.c. daily, which was followed by a reticulocyte rise to 12 per cent. After the red blood cell count reached approximately 4.00 million per cu. mm., the patient was given weekly injections of liver extract intramuscularly, 8 c.c. (Parke, Davis & Co.) and in addition she received vitamin B orally. Her red blood cell count when last seen on February 2, 1938, was normal, as well as her hemoglobin, and there had been a gain in weight of 29 pounds since the patient was first seen. The response of her blood to treatment is shown in chart 7.

Case 8. W. T. M., a male, 40 years of age, was admitted November 16, 1931 with the chief complaint of "abdominal pain."

Present Illness: In January 1930 the patient first noted abdominal cramps and sharp shooting pain below the right rib margin. This pain came in attacks and persisted for about two hours. Once it was accompanied by vomiting, diarrhea and jaundice which persisted for one week. The patient has had a number of such attacks.

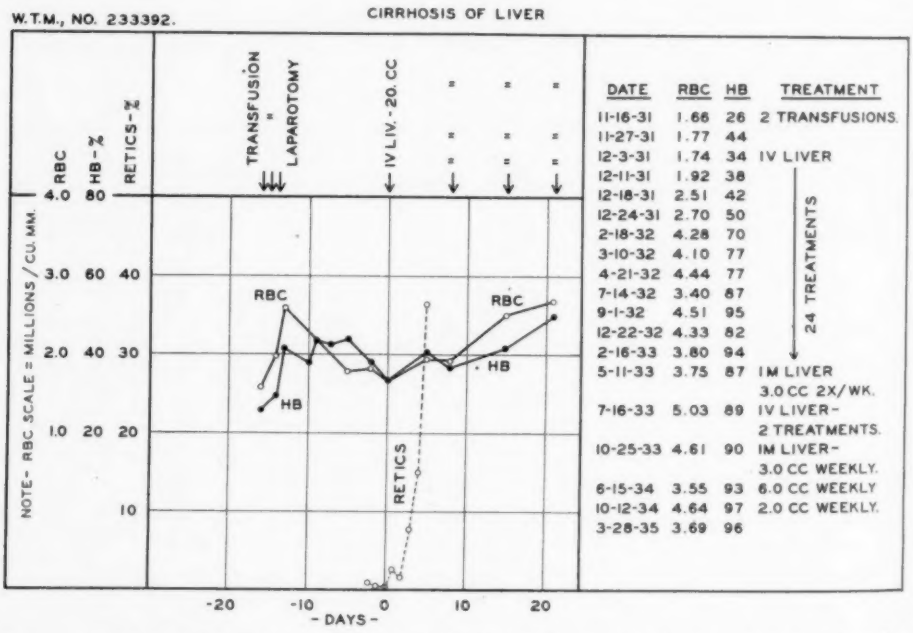

CHART 8. The hematologic response in cirrhosis of the liver following the administration of parenteral liver extract.

Physical Examination: There was very definite evidence of weight loss, and the skin was icteric. The liver was moderately enlarged and there was tenderness in the upper quadrants. The spleen was barely palpable. The red blood cell count was 1.66 million per cu. mm., hemoglobin 26 per cent. The roentgen-ray examination was negative. The patient was thought to have some type of abdominal malignant growth and as a result exploratory laparotomy was done on November 19, 1931. No neo-

plasm was noted but the patient was found to have a definite cirrhosis of the liver. Two blood transfusions were given and later intravenous liver extract was administered. As a result, there was a prompt increase in the reticulocytes which reached a peak of 36 per cent, at which time the patient left the hospital. Subsequently, with additional intravenous treatments of liver extract and later with intramuscular treatments, the blood returned to normal. The blood was not maintained continuously at a normal level because the patient received some experimental liver extract which possibly was not of full potency, and later he administered the treatments himself and became lax in following directions. The response of his blood to treatment is shown in chart 8.

Case 9. R. M., a male, 55 years of age, was admitted October 29, 1931, with the chief complaint of "pain in the abdomen."

Present Illness: The patient complained that he had suffered from abdominal discomfort below the umbilicus for three months prior to admission. It was generalized and gradually became more severe. Also he had been troubled with nausea but there had been no vomiting. A short time before admission he had developed moderate dyspnea and palpitation on exertion. There had been a 10 pound weight loss.

Physical examination showed evidence of weight loss. The abdomen was mod-

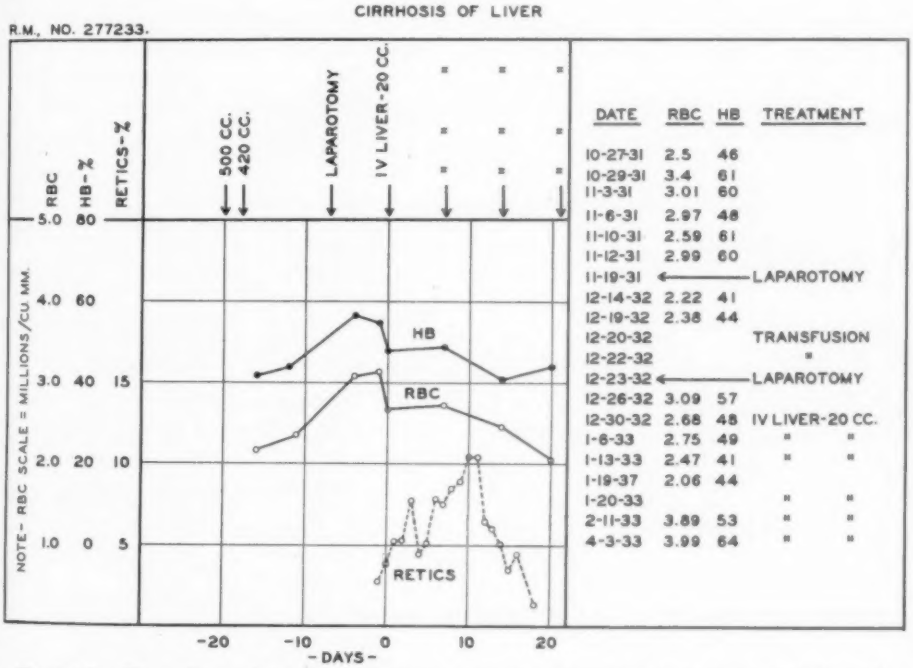

CHART 9. The effect of intravenous liver extract on hematopoiesis in a patient with hepatic cirrhosis.

erately distended and there was generalized tenderness. Slight pitting edema was present. The red blood cell count was 2.51 million per cu. mm., hemoglobin 46 per cent. Gastric analysis showed free hydrochloric acid present. The patient was thought to have an abdominal malignant growth and this diagnosis led to a laparotomy on November 19, 1931. No neoplasm was found but the patient was observed to have cirrhosis of the liver. About one year later the patient returned stating that he had had a recurrence of all his symptoms which had troubled him for the previous

six months. Physical examination was the same as on previous admission. Roentgen-ray examination at this time showed what was considered to be an obstructive cancer of the transverse colon. The red blood cell count was 2.22 million per cu. mm., hemoglobin 41 per cent. On December 23, 1932 laparotomy was performed and the defect observed in the roentgen-ray was found to be due to marked adhesions at the hepatic flexure. A few days after the operation he was given injections of liver extract intravenously which caused a reticulocyte response and an increase in the red blood cells to approximately 4.00 million, and of the hemoglobin to 64 per cent. He was last seen on March 3, 1933, and his present condition is not known. The changes in the blood following treatment are shown in chart 9.

Case 10. R. J., a female, 32 years of age, was admitted to the hospital on March 22, 1937 with the chief complaints of dyspnea, palpitation and weakness. Four and a half months before admission, at which time the patient was seven months pregnant, she had developed dyspnea on exertion, mild generalized abdominal pain and had noted a few purpuric areas around the umbilicus. At this time a marked pallor appeared. The red blood cell count was said to be 2.00 million per cu. mm. at that time. She was treated with "Ventriculin and Iron" and by two transfusions, and improved somewhat. At the eighth month of pregnancy her red blood cell count was reported as being 1.80 million per cu. mm. Labor was induced at this time. Following this the dyspnea, palpitation and weakness increased and she was treated with transfusions, intramuscular liver extract and iron. There was a 10 pound weight loss.

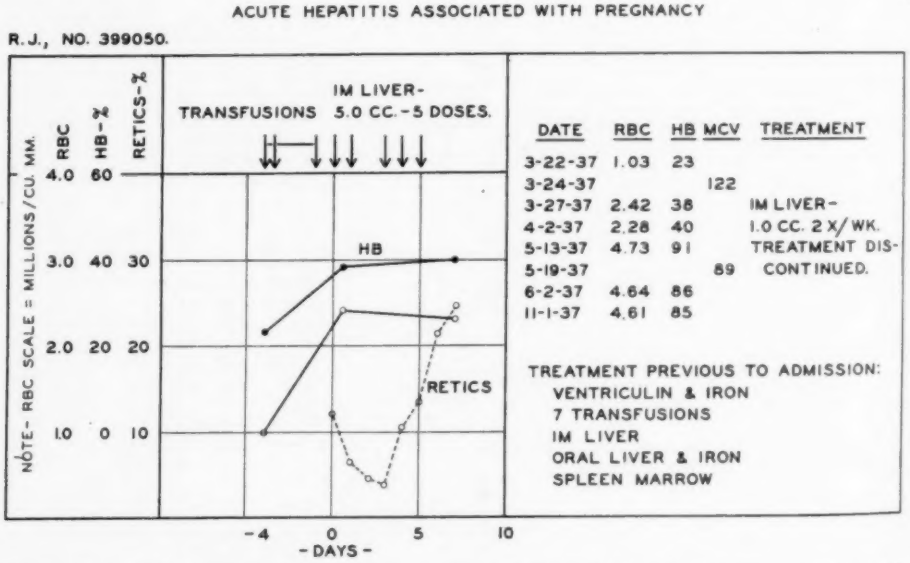

CHART 10. An induced remission due to parenteral liver therapy in the macrocytic anemia associated with acute hepatitis.

Physical examination showed a pale, emaciated female. The liver reached the level of the umbilicus and the spleen descended 4 cm. below the left costal margin. There was pitting edema of the ankles. The red blood cell count was 1.03 million per cu. mm., hemoglobin 23 per cent. Bilirubin 1.5 mg. per 100 c.c. Mean corpuscular volume 122 cu. microns. Gastric analysis following administration of histamine revealed an absence of free hydrochloric acid. Sternal puncture showed increased erythrogenesis. Patient was thought to have an acute hepatitis associated with

pregnancy and the liver disturbance was considered to be the cause of the anemia. She was treated with three blood transfusions and at the same time given intramuscular injections of liver extract (Parke, Davis & Company) 5 c.c. daily for three days. At the end of this time the reticulocytes rose to 21.5 per cent; the patient felt much improved and she left the hospital. Subsequent blood examinations showed the blood had returned to normal. She had been receiving intramuscular liver extract 1 c.c. two times weekly but after the blood was found to be normal, May 13, 1937, her anti-pernicious anemia therapy was discontinued. The changes in the patient's blood are shown in chart 10.

Discussion

The question might be raised quite properly concerning the causal relationship between the gastric lesion and the macrocytic anemia. It is, of course, possible that, in some instances there might be a coincidental association of the two conditions and no etiological relationship. Studies to determine the presence or absence of the intrinsic factor in the stomach would shed some light on this question but unfortunately it was possible to determine this only in Case 5, in which this factor was found to be absent. Its absence was interpreted as being due to an extensive malignant involvement (linitis plastica) of the entire stomach and a destruction of the gastric secreting glands which produce the intrinsic factor. One reason which indicates that intestinal lesions are responsible for this type of anemia is the disappearance of the anemia when the intestinal lesion is repaired. In Case 7, for example, the red blood cell count returned to normal following resection of the small intestine for partial obstruction, at which time the patient was not receiving any anti-anemic therapy. It is also of significance that the anemia reappeared when the partial obstruction again developed.

Further evidence that the group of patients which was studied did not have a true Addisonian anemia which by chance was associated with some gastrointestinal lesions is that three of the 10 patients considered had free hydrochloric acid present in the gastric secretions (table 1). Also five of the seven patients about whom information was obtained did not have paresthesia of the hands and feet which is present in 90 per cent of patients with pernicious anemia. Furthermore, only one patient had recurrent glossitis, which is present in approximately 65 per cent of patients with Addisonian anemia. In eight patients where data were recorded, a definite statement is made saying that there was no atrophy of the tongue. This sign is present in about half of the patients with pernicious anemia.

The action of autolyzed yeast (Vegex) on the reticulocytes, red blood cells and hemoglobin of a patient with typical pernicious anemia is shown in chart 11. The fact that some patients with pernicious anemia show an improvement following the ingestion of this substance is of more theoretical than practical interest since more satisfactory therapeutic results are obtained by the administration of liver and stomach preparations. The mode of action of yeast in these patients is not clearly understood. Ungley [23, 24, 25] considers that it probably acts by virtue of its content of extrinsic factor and

TABLE I

Pt.	Case No.	Sex	Age	Nature Oper.	Time before Anemia Disc.	RBC Mill.	Hb. %	Achlorhydria	Glossitis	Atrophy Tongue	Paresthesia Hands and Feet	Vibr. Sense	Mot. and Pos.	Resp. to Therapy	Type of Therapy	Diagnosis
VM	1	F.	27	Partial resect. stomach	33 mos.	1.2	23	Yes	No	No	No	N	N	Good	I. V. Oral Liv. Ext.	Gumma stomach
AF	2	M.	38	Partial resect. stomach	29 mos.	1.8	40	Yes	No	No	No	N	N	Good	I. M. Liv. Ext.	Cancer stomach
JK	3	M.	53	Partial gastrec.	30 mos.	2.8	79	—	—	—	—	—	—	Good	I. M. Liv. Ext.	Cancer stomach
JGK	4	M.	63	None	—	1.3	32	Yes	No	No	No	N	N	Good	Ventriculin	Linitis plastica
MRN	5	F.	46	3 short circuit. Op.	5 yrs.	3.3	70	Yes	No	No	—	N	N	Good	I. M. Liv. Ext.	Multiple anastomoses bowel
CH	6	M.	31	Resect. intestine	—	2.7	63	No	No	No	No	N	N	Good	I. M. Liv. Ext. Vegex	Reg. ulcer; ileitis
MP	7	F.	52	Lap.[1]	—	2.5	53	No	Yes	No	Yes	Dim.	N	Good	I. M. Liv. Ext.	Ileocolic fistula
WTM	8	M.	40	Exp. lap.	—	1.7	26	Yes	—	No	—	N	N	Good	I. V. I. M. Liv. Ext.	Cirrhosis liver
RM	9	M.	55	Two exp. lap.	—	2.5	46	No	No	No	Yes	N	N	Good	I. V. Liv. Ext.	Cirrhosis liver
RJ	10	F.	32	None	—	1.0	23	Yes	No	—	No	N	N	Good	I. M. Liv. Ext.	Acute hepatitis

[1] An unsuccessful attempt to relieve ileo-colic fistula.

cites observations which he had previously reported showing that it is not effective when administered parenterally. On the other hand, Davidson [26] concludes that autolyzed yeast contains some hemopoietic principle. Russell [27] suggests that small amounts of the intrinsic factor are present in the

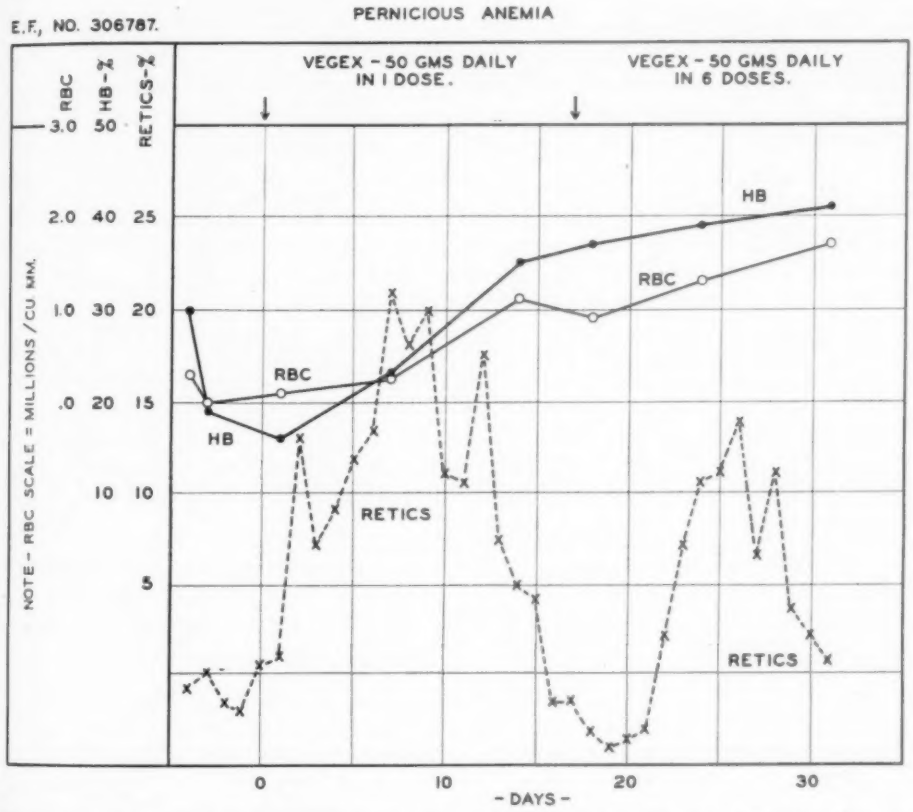

CHART 11. The action of autolyzed yeast (Vegex) on the reticulocytes, red blood cell count and hemoglobin of patients with pernicious anemia.

gastric secretion in some patients with pernicious anemia (and this has been substantiated by Goldhamer [11]), and that some red blood cell maturing substance is produced when large amounts of the extrinsic factor are administered in the form of yeast.

It is not difficult to understand why a macrocytic anemia develops in some patients following partial resection of the stomach. The intrinsic factor which is essential to maturation of the erythrocytes is undoubtedly secreted by the glands in the gastric mucosa. Meulengracht's work [6, 7, 8, 9] indicates that the glands of the pylorus are the most effective in this function, whereas those of the fundus are ineffective and those of the cardiac end of the stomach are only slightly active. He considers also that the active secreting glands are present to some extent in the duodenum. It appears to

be a logical assumption that the development of a macrocytic anemia following operations on the stomach depends almost entirely on how much of the stomach remains following the operation.

The association of this type of anemia with the presence in patients of multiple intestinal anastomoses can readily be explained on the ground that the intestinal contents may pass through only a small portion of the small intestines in such cases and, therefore, the likelihood of absorbing a normal amount of the active principle would be diminished. It is somewhat more difficult to understand why an intestinal stricture or partial obstruction, such as existed in Case 7 of our series should develop a macrocytic anemia, as only a relatively small portion of the small intestine was involved in the pathologic process. A plausible assumption would be that even a localized lesion may in some manner affect the entire intestinal tract in such a way as to destroy or prevent the absorption of the active principle.

The relation of liver disease to the development of macrocytic anemia is thought to be due to the failure of this viscus to function as a storage depot for the active principle which, as a result, cannot be released in an orderly fashion as required to control the maturation of the erythrocytes in the bone marrow. It is assumed in such cases that although the active principle is formed in the stomach and absorbed from the intestine, it cannot be stored in a liver which is extensively damaged and it is lost, therefore, from the body, possibly through the kidneys.

An interesting point for discussion is the length of time required for a macrocytic anemia to develop following resection of the stomach, or after the development of intestinal lesions. Although the information available is incomplete and may not be strictly accurate, all indications are that the anemia does not reach a stage severe enough to produce symptoms for a period of two to five years or longer. The length of time elapsing varies according to several factors. First, it is dependent upon the extent to which the gastric and intestinal function is impaired; it is affected, secondly, by the amount of reserve erythrocyte maturing material which is stored in the liver and perhaps elsewhere in the body. Other conditions which may possibly be of importance are the age of the individual and the presence of infections. These factors are considered because it is known that patients with pernicious anemia who are elderly and those who develop an infection have an increased requirement of the erythrocyte maturing substance. This is known because larger doses of anti-pernicious anemia medication are required to maintain their blood at a normal level. It would seem logical to assume, therefore, that following a gastrectomy, for example, the reserve supply of the active principle would be consumed more rapidly if the patient were elderly or had an active infection, and that on this account a macrocytic anemia would develop more quickly in such a patient.

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TOLERANCE AND TOXICITY OF INSULIN

II. WITH FORCED ADMINISTRATION OF CARBOHYDRATE*

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WHEN insufficient carbohydrate is eaten to protect against insulin, there is naturally a recourse to forced administration of glucose either by stomach or parenterally. In dealing with large doses it is necessary to take account of the toxicity of glucose, though there seems to be no positive information as to whether the injury is entirely physical (osmotic) or whether there is an additional chemical action.

GLUCOSE CONTROLS

The writer (1913) published the first experiments with prolonged administration of various sugars by various channels, with a view to the diabetogenic influence and also other possible effects of chronic hyperglycemia. Regarding the first, it was established that the digestion or the constitutional strength always breaks down before the pancreatic island function, not only in normal animals but also in those depancreatized to any degree short of diabetes. The dividing line is so sharp that a point is reached where removal of a fraction of a gram of pancreatic tissue makes the animal diabetic and therefore subject to the breaking down of its tolerance with sugar; but without the removal of this final trifle of tissue there is only a moderate reduction shown in assimilation tests and no amount or duration of sugar feeding can bring on diabetes. Other observations made by the writer and by others about that time can now be reinterpreted as evidence that the ordinary death from starvation is due to hypoglycemia, since the feeding or injection of glucose, or the giving of a diet deficient in both protein and calories, at the extreme end of starvation suffices to prolong life by a number of days. The still unsettled question of the effect of long-continued moderate hyperglycemia cannot be answered by administration of glucose to normal animals, because the large doses required break down digestion or general health, perhaps from osmotic causes alone. In order to minimize this factor and also imitate the condition of a continuous circulating excess of an almost unutilized sugar, such as is encountered in diabetes, cane sugar was injected subcutaneously over long periods, the most striking effect being the production of a peculiar obesity combined with imbecile mentality in a cat. This effect upon the nervous

* Received for publication February 26, 1938.
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Reference may be made to the first paper of this series concerning the effect of insulin with spontaneous eating (New England Jr. Med., July 21, 1938).
† With the technical assistance of James H. Rice.

system may be worth further investigation. The writer shares the view of a number of clinicians that a marked excess of blood sugar in diabetic patients is unphysiological and in the course of years may be suspected of responsibility for neuritic pains or general tissue damage, possibly through slight disturbances of hydration or other processes which at present are not accurately understood.

Gigon (1924) fed glucose or levulose to several species of animals for periods up to several months, with the general result of malnutrition. Bouckaert and collaborators (1934) injected rabbits with 200 or 300 c.c. of 10 per cent glucose solution per day, the average result being death in 3½ days. This was not due to hyperglycemia because it was not preventable by insulin. It was shown by blood analyses to be due to deficiency of circulating chloride, and it was preventable by saline injections.

Large doses of glucose can be given with less osmotic injury intravenously, than subcutaneously or otherwise. Mazzola and Torrey (1933) tested the effect of various single injections from the standpoint of shock. The ideal method, namely continuous intravenous infusion (developed especially by Woodyatt), was used by Butsch (1934). He was thus able to give dogs 3 gm. of glucose per kg. per hour, finding at the end of 36 to 51 hours a sharp break in tolerance as indicated by increased hyperglycemia and glycosuria. There were maximal glycogen deposits, up to 20 per cent in the liver and 2.5 or 3.5 per cent in the muscles. It was possible to continue the injections for 6 to 18 hours longer and demonstrate retention of the same percentages of glycogen; in other words, a break in tolerance in the sense of diabetes was not evident. Jacobs and Colwell (1936) used a continuous slow infusion of 50 per cent glucose in order to give a minimum of surplus water. With injections at rates of 0.7 to 4.5 gm. glucose per kg. per hour, the longest survival was 166 hours. Stained sections showed heavy glycogen but also lesions in various organs. It was concluded that the experiments "show that the continuous administration of glucose even at rates just within the limits of tolerance, that is, not causing glycosuria, is always fatal," while injections at higher rates are more rapidly fatal.

The production of fatal osmotic shock by intraperitoneal injections of either hyper- or hypotonic salt solutions was illustrated by Doménech-Alsina (1932). Gilman (1934) showed similar results with isotonic 5.5 per cent glucose solution, as the result of diffusion of electrolytes out of the blood.

The unavoidability of the osmotic injury with large doses of glucose must be recognized with all methods, since the solution is necessarily either hypertonic before assimilation of the glucose or hypotonic afterward. For example, table 1 shows that 25 gm. glucose in 50 per cent solution by stomach tube is fatal to rabbits, more acutely if the dose is repeated within a few hours. Though the osmotic injury of the strong solution alone is disastrous, other tests have shown severe disturbances from administration of this amount of glucose in any concentration.

TABLE I

Glucose Controls

Animal Groups	Weight kg.	Treatment	Range of Minimum Blood Sugars mg. %	Range of Red Cell Counts Millions	Result
4 rabbits	2 kg.	25 gm. glucose in 50% solution by stomach tube, once or repeated in 4 hours.	140–760	6.9–12.5	Prostration. Death in 3 hours to 2 days.
2 rabbits	1.8 kg.	3 subcut. injections of 50 c.c. 20% glucose at 4-hour intervals.	120–575	6.1–8.9	Collapse. Death in 18 hours with fever up to 107° F.
1 rabbit	1.7 kg.	3 subcut. injections of 200 c.c. 5% glucose in water, at 4-hour intervals.	122–480	8.3–3.5	Progressive weakness. Death in 15 hours.
2 rabbits	1.5 kg.	3 subcut. injections of 100 c.c. 10% glucose in saline, at 4-hour intervals.	110–360	6.2–7.4	Temporary weakness. Recovery.
5 rabbits	1.5 to 2 kg.	20 to 30 gm. glucose in 10% solution in saline, divided in 2 to 10 subcut. injections daily during fasting.	120–150	7.6–5.3	Death from weakness in 3 to 9 days, while controls fasting without glucose survived.
2 cats	2 kg.	3 injections of 70 c.c. 20% glucose subcut. at 5-hour intervals.	130–540	7.5–13	Weakness. Death within 24 hours.
2 cats	2 kg.	3 injections of 140 c.c. 10% glucose subcut. at 5-hour intervals.	140–370	7.8–6.3	Temporary weakness. Recovery.
4 cats	3.5 to 4 kg.	300 to 450 c.c. 10% glucose solution, divided into 2 to 5 injections subcut., daily during fasting for 10 days.	160–420	6.8–9.3	Survival. Precisely the same loss of weight as controls fasting without glucose, but apparently less strength.

In table 1, it is seen that rabbits and small cats can be killed by the subcutaneous injection of 30 to 40 gm. of glucose in the course of 12 to 15 hours, whether hypertonic (20 per cent) or isotonic (5 per cent) solutions in water are employed. The identical quantity of glucose in 10 per cent solution in saline or Ringer solution was not fatal. On the basis of this and other trials, the last mentioned solution was adopted for routine use.

As the insulin experiments frequently involved administration of considerable glucose to animals during a series of days of fasting, the tables illustrate controls of this kind. Rabbits receiving 20 to 30 gm. daily (notwithstanding division into as many as 10 injections in 24 hours to reduce osmotic shock) died in three to nine days, while the fasting controls survived. Cats, being stronger, survived for 10 days without obvious harm from 30 to 45 gm. glucose per day, but also without benefit. Two points may be noted incidentally. (*a*) Some of these animals were kept hyperglycemic throughout the entire period, 24 hours every day; the blood

sugars shown range as high as 575 mg., and in experiments not shown it has been temporarily as high as 1500 mg. The essential injury is not due to hyperglycemia, because it occurs under the identical conditions when the blood sugar is reduced with insulin. (*b*) The strengthening effects of glucose injections, so readily demonstrable in brief trials experimentally and clinically, do not continue with prolonged repetition. According to all available evidence, attempts at parenteral nutrition with glucose during prolonged fasting are harmful rather than helpful. Therefore the benefits of continuous hyperglycemia as imagined by a number of clinicians, on account of glycogen formation, cardiac stimulation, etc., are contrary to the established facts in normal animals. The obvious difference between the endogenous hyperglycemia of diabetes and the induced hyperglycemia in the normal organism leaves the question of harm to the diabetic still open. But as far as any argument can be based upon glucose administration, the proof is positive that nature makes utmost efforts to keep the blood sugar within normal limits and that any prolonged violation of these limits is harmful, not because of the hyperglycemia itself but because of associated processes.

Glucose and Insulin Administration

Investigation of the specific toxicity of insulin requires the administration of large doses of insulin together with the prevention of hypoglycemia by means of non-fatal doses of glucose.

Crystalline insulin was not used in the present experiments. The kindness of Dr. M. Sahyun of Stearns & Co., in furnishing a supply of the "impurities" of commercial insulin, made possible a number of control tests showing that the results obtained with insulin are not due to foreign substances in the commercial preparation.

Attempts at chronic insulin poisoning were made by Gigon (1924–25), who gave rabbits 10 to 15 units daily and checked convulsions by injections of 10 to 20 c.c. of 20 to 40 per cent glucose. Death occurred in 4 to 23 days. The need for the glucose injections is not clear, since rabbits readily tolerate such small insulin doses with spontaneous eating. Likewise the fatal outcome was probably due to malnutrition rather than to any direct effect of the insulin. Also Dünner, Ostertag and Thannhauser (1933) used dogs, rabbits and guinea-pigs. Their "small" doses were 2 to 4 units, but the amount of the "large" doses is not mentioned. After nervous symptoms, depression and malnutrition for eight weeks a dog was found unconscious with normal blood sugar. Examinations after death showed various organic lesions, glycogen-free liver and glycogen-poor muscles. On the other hand Long and Bischoff (1929) started rabbits at three months of age on 6 to 14 units of insulin daily, and in observations of more than six weeks found nothing more than a failure to gain weight beyond the controls. From this and other work it may be concluded that a state of chronic insulin poisoning has never been demonstrated.

Investigation of the toxicity of large doses in acute experiments was

attempted by Loeb, Nichols and Paige, who, using 2 kg. rabbits, injected 75 units of insulin per kg. intravenously and repeated the same in four hours. According to internal evidence in the paper, these young authors carried out the actual procedures accurately but fell into certain errors in planning their experiments. Three of such errors may be cited: (1) The observations were terminated 7½ hours after the first, 3½ hours after the second insulin dose. The principal effects, namely the delayed ones, were thus missed entirely. Even with reference to their primary problem, namely the possible toxicity of high insulin doses in diabetic coma, there was no reason to assume that the treatment or the results are finished within an 8-hour day. (2) On the assumption that their supposedly huge dosage must be balanced by equally huge amounts of glucose, they gave 12 gm. of glucose per kg. in 50 per cent solution by stomach tube after each insulin injection, without any control experiments to ascertain whether such a dosage is in itself not fatal on account of both quantity and concentration, and whether much smaller amounts would not suffice to balance the insulin. (3) After only 7½ hours some rabbits were dead, many others were dangerously weak; all were then killed after this insufficient period of observation, and the conclusion was drawn that insulin is non-toxic. The uncritical acceptance of this conclusion seems to constitute the only basis for the prevailing view of the non-toxicity of insulin apart from hypoglycemia.

Experiments.—Parenteral Glucose with Insulin

1. Efficiency

In general, it is possible even with the most enormous insulin doses to save an animal by a small subcutaneous injection of glucose at the very beginning of convulsions or collapse, the absorption being rapid enough to halt the attack. This was the method used routinely, supplemented if necessary by intramuscular and intraperitoneal injections.

Intravenous injections, being the most rapid and precise in effects, permit of a slight saving of glucose in comparison with the other methods. A convulsion resulting from 50 units of insulin in a rabbit can be checked with as little as 0.2 to 0.4 gm. of glucose by vein; such protection may last from a few minutes to half an hour, depending upon the stage of the process. A rabbit was completely protected against a subcutaneous dose of 50 units by means of repeated small intravenous injections totalling 5.9 gm. of glucose in 10 hours.

2. Insufficient and Excessive Glucose

It is well known that animals can sometimes remain in serious hypoglycemia for a considerable period without violent seizures. When convulsions or collapse finally appear, glucose may fail to save life, and such a death can be attributed to insufficiency of glucose from an early stage. The temptation therefore exists to go to the opposite extreme by supplying

TABLE II

Rats—Insulin with Parenteral Glucose Injections

No. of animals	Weight gm.	Insulin units subcutaneously	Hours before first reaction	Glucose in first 6 hrs. gm.	Glucose in second 6 hrs. gm.	Glucose in second 12 hrs. gm.	Total glucose required gm.	Total hours of treatment	Final blood sugar mg. %	Result
6	130–240	10–30	2½–4	0.6–0.9	0.5–0.8	0	1.2–1.6	8–12	60–110	Comfortable; lived
8	120–225	40–80	2¼–3	0.9–1.3	0.7–1.2	0.5–0.9	1.9–3.3	16–24	52–140	Slight depression; lived
6	110–220	100	2–3⅙	0.9–1.5	1.1–1.4	0.4–1.3	2.6–4.0	15–24	78–190	Slight depression; lived
6	125–240	150	1¾–2¾	1.4–1.8	1.2–1.6	1.0–1.5	3.5–4.6	20–26	56–210	Depression; lived
4	110–200	200	2 –2¾	2.0–4.0	1.8–2.8	1.6–2.0	5.0–6.6	18–30	48–181	Weakness; lived
5	140–320	250	1½–3	0.4–2.8	0.4–3.0	2.3–3.5	2.5–12.4	21–42	40–234	Weakness; dyspnea, death
1	110	300	—	2.5	1.8	—	4.3	10	256	Rapid weakness; death
1	270	325	3	0.5	1.0	1.0	3.5	20	90	Recovered
1	300	400	2½	1.3	2.0	1.0	7.3	34		Weakness, dyspnea, death
1	190	800	1¾	1.5	1.0	0.5	3.0	15		Weakness, dyspnea, death
		Intravenously								
3	120–215	10–30	2 –3¼	0.4–0.8	0	0	0.4–0.8	6	52–76	Comfortable; lived
5	115–210	40–80	1¾–2¾	0.5–1.2	0.9–1.2	0 –0.4	1.5–2.7	12–15	81–157	Slight depression; lived
4	110–200	100	1¼–2½	0.9–1.5	0.8–1.1	0.8–1.4	2.6–3.8	16–20	42–198	Three died, one survived
3	120–180	150	1½–2¼	1.3–1.7	1.4–2.0	0.5–1.0	3.4–4.6	13–17	38–250	Weakness, dyspnea, death

TABLE III

TABLE III

Other Species—Insulin with Parenteral Glucose Injections

Animals	Weight kg.	Insulin units	Hours before first reaction	Total glucose required	Hours of treatment	Initial erythrocyte count. Millions	Final erythrocyte count. Millions	Final blood sugar mg. %	Result
		Subcutaneously							
4 rabbits	1.8–2.2	50	2¾–3¼	10–13	9–12	7.7	9.8	62–98	Comfortable; lived
2 rabbits	2	100	2½–3	17–21	11–15	6.3	7.3	75–194	Depression, lived
4 rabbits	1.9–2.3	150	1½–2¼	21–25	16–24	—	—	88–165	2 lived; 2 died
2 rabbits	2.0–2.1	150 repeated in 4 hrs.	1¾–2	98–106	74–100	6.9	2.2	180–224	Weakness, dyspnea, death. Trace of glycogen in liver, heart, skeletal muscles
6 rabbits	2.0–2.3	200	1¼–3	28–42	16–36	8.1	4.0	115–288	1 lived, 5 died
6 rabbits	2.0–2.4	250	1½–3½	21–44	19–29	—	—	120–214	5 died under treatment; 1 died in sudden convulsions 12 hrs. after last glucose injection
3 rabbits	2.3–2.6	300	1¼–1½	17–35	10–34	—	—	—	2 died under treatment; 1 died in convulsions 20 hrs. after last glucose injection
		Intravenously							
5 rabbits	1.7–2.1	50–100	1 –1¼	7–12	7–9	—	—	52–184	Slight depression; lived
4 rabbits	1.8–2.3	150	1¼–1½	8–15	10–14	7.9	6.1	79–194	Depression; lived
4 rabbits	2.0–2.3	150 repeated in 4 hrs.	1 –1¾	13–24	9–22	7.0–8.0	3.1–5.8	103–360	2 lived, 2 died (liver glycogen-free)
2 rabbits	2.1–2.3	150 repeated in 4 hrs. 2nd day	¾–1	18–26	13–17	4.1	2.8	190–235	Weakness, dyspnea, death
3 rabbits	2.0–2.6	200	1¼–1½	8–18	7–16	—	—	84–600	1 lived, 2 died
		Subcutaneously							
4 cats	3.0–4.0	50–100	4 –5¼	7–9	8–10	7.6	9.2	52–170	Slight depression; lived
5 cats	2.5–3.5	200–500	3¾–4½	15–24	18–26	—	—	87–320	Weakness; lived
3 cats	2.2–3.2	800	3½–5	16–28	28–44	—	—	70–1400	Weakness; lived
5 cats	2.8–4.0	1000	2½–4½	8–20	16–21	7.9	11.3	66–484	4 lived, 1 died
4 cats	3 –3.8	1200–1500	2 –3½	12–22	14–22	—	—	107–208	Died
1 dog	10	2500	3¼	190 (114 by vein and 76 subcutaneously)	55	5.3	3.1	180	Progressive weakness, dyspnea, minor and major spasms, death

glucose liberally from the outset, so as to prevent all symptoms from beginning to end. With the largest insulin doses, involving the longest treatment, this method results in killing some animals with glucose, when those which receive less sugar survive. In general, it has seemed best to await the first signs of a beginning attack and then check it by a small subcutaneous injection of 10 per cent glucose in saline or Ringer solution (usually 2 to 5 c.c. for rats, 10 to 20 c.c. for rabbits or cats). A long series of such brief convulsions seems to be not dangerous, even when continued through several days. At the same time numerous quick blood sugar analyses are necessary, for information concerning unsuspected hypoglycemia or the dyspnea and convulsions which sometimes occur with marked hyperglycemia.

Deaths resulting either from hypoglycemia or from excessive glucose are not instructive for the present problem. Accordingly, many animals were not suitable for inclusion in tables 2 and 3. The data in the vertical columns of these tables will now be discussed in succession.

3. Animals. Weight

In only a few trials were matched animals or litter-mates used. Many were used immediately after being received, and others after long stay in the laboratory. Animals of similar size and apparent strength frequently differ in their response to insulin doses, for unknown reasons. There is not even a consistent relationship with the body weight. The factor of strength, however, deserves emphasis. Animals weak or sick from any cause are markedly subnormal in insulin tolerance.

4. Insulin Dosage

Rats are the only species thus far tested having a higher insulin tolerance with spontaneous eating than with parenteral injections.* Incidentally, it should be understood that mixed programs are possible, and rats which have stopped eating with huge insulin doses may sometimes be revived by parenteral injections, and then resume eating and survive.

With insulin and glucose both given subcutaneously, the tolerance limit of ordinary sized rats seems to be 200 units, with which a majority died. One large animal survived after 325 units. With as little as 150 units, there were two deaths out of four, in addition to a larger number from hypoglycemic accidents not tabulated.

The high mortality of rats from insulin given intravenously, beginning at 100 units and becoming 100 per cent at 150 units, is probably due to accidental or extraneous factors, such as impurities or the larger volume (U 40 commercial insulin being used). It was not connected with any special difficulty of keeping up the blood sugar level, and it was contrary to the results in larger species.

The larger species survive far higher insulin doses with parenteral glucose injections than with spontaneous eating.

* Work to be published subsequently indicates that this is true also for the guinea pig.

Following the plan of Loeb et al., it is found that rabbits can survive 150 units of insulin intravenously, and at least some of them can survive this dose repeated in four hours, provided they are not killed by excess of glucose. But as regards application to diabetic therapy, which in acidosis often requires high insulin on more than one day, it must be noted that the above dosage is fatal to rabbits when repeated on a second day. Also in practice insulin is generally administered subcutaneously rather than intravenously, and the subcutaneous injection of 150 units repeated in four hours is fatal to rabbits.

Apparently the upper limit of insulin tolerance in rabbits is from 150 to 250 units either subcutaneously or intravenously, in other words about equal in absolute values to the tolerance of rats. The intravenous injections are

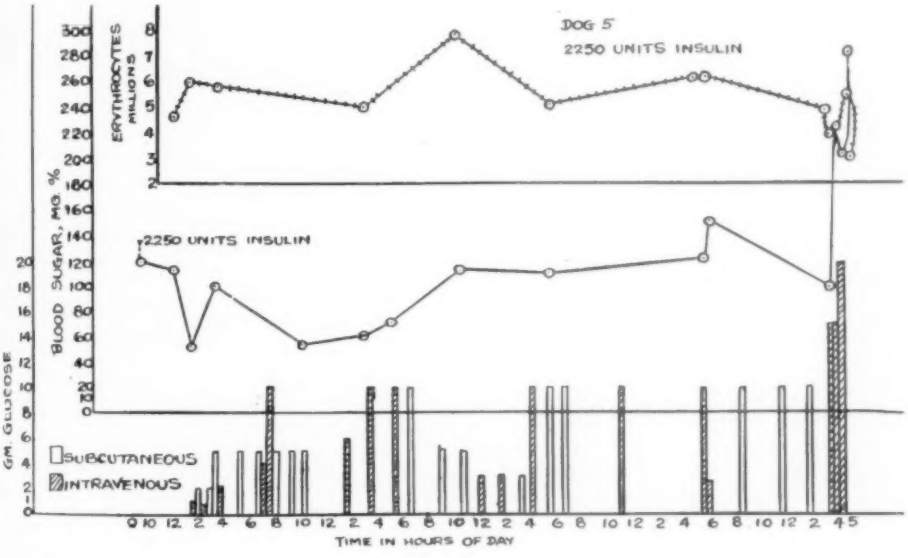

FIG. 1.

less dangerous (as illustrated particularly by the ability to repeat the 150-unit dose intravenously but not subcutaneously) but also less powerful as judged by the briefer duration and the smaller amount of glucose required for antidoting.

Cats of average size proved able to tolerate 1,000 to 1,200 units subcutaneously but not 1,400 units or higher doses.

Several observations on dogs may be described at this point, as follows. The 10 kg. animal in table 4 is represented in greater detail in figure 1, which shows in particular that the death could not be attributed to hypoglycemia.

The 14 kg. animal depicted in figure 2 survived an insulin dose of 2,000 units (in the Psychiatric Institute). Here the toxicity of glucose was minimized by the use of minimal quantities. No attention was paid to hypo-

TABLE IV

Food and Glucose Administration after Insulin Injections in Rabbits

Rabbit No.	Insulin subcut. units	Food by stomach		Glucose subcut. gm.	Duration of treatment hours	Result
		Voluntary	By tube			
1	250	130 gm. lettuce, 10 gm. bread, 10 gm. oats	50 c.c. milk, 100 c.c. 10% glucose	20	40	Progressive weakness; death.
2	250	25 gm. bread	300 c.c. milk	2	24	Recovery.
3	250	—	260 c.c. 10% glucose	21	45	Appeared well at end of treatment; died later when unwatched, presumably from delayed hypoglycemia.
4	250	—	350 c.c. 10% glucose	2	14	Fasting afterward, remained symptom-free.
5	350	20 gm. carrots, 5 gm. oats	100 c.c. 10% glucose	22	32	Moderately weak at end of treatment; died later when unwatched.
6	400	—	300 c.c. milk, 50 c.c. 10% glucose	8	19	Fasting after treatment, symptom-free. Recovery.

glycemia, except that whenever a convulsion began 10 gm. of glucose were immediately injected intravenously. Although the last of these active seizures occurred 30 hours after the insulin injection, it is noticeable that distinct hypoglycemia lasted into the third day. Only on the fourth day the blood sugar rose to a level slightly above normal for a fasting animal.

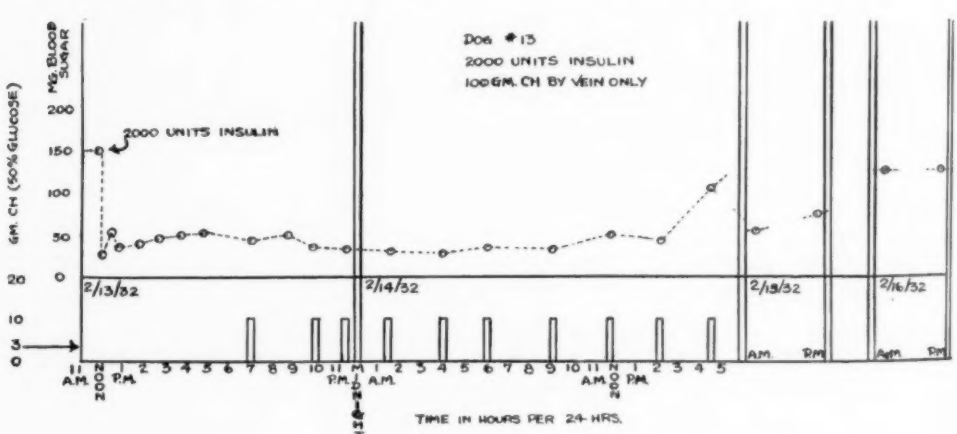

FIG. 2.

A third experiment was carried out on a 4 kg. dog with the coöperation of Drs. Barckley, Blum, Ferraioli, Kastle, Kemp, Saxe and Shetter of the Polyclinic Hospital staff. Instead of the insulin being given in a single huge injection, it was begun with a dose of 400 units followed by injections every hour or two, diminishing gradually to 100 units, then 50 units and

finally 20 units each, all subcutaneously, so as to maintain a constant inflow rather than a single sudden flood of insulin. The total time from the first injection to death was 57 hours. In this way the insulin dosage amounted to 1900 units in the first 24 hours, 800 units in the second 24 hours, and 100 units in the remaining 9 hours, making a total of 2800 units, or 700 units per kg. Also a continuous intravenous infusion of 10 per cent glucose in Ringer solution was given, beginning at 100 c.c. per hour and reduced as needed, down to as low as 50 c.c. per hour during much of the time. Also during two periods totalling 14 hours the tube was withdrawn from the vein altogether and the blood sugar was kept up by small subcutaneous injections. Frequent analyses proved that the blood sugar was thus maintained between the limits of 110 and 360 mg., with a single exception of 600 mg. According to the experience of Butsch, also Jacobs and Colwell, such glucose injections are non-fatal, and the death must therefore be attributed to an action of the massive insulin dose, other than hypoglycemia.

5. Interval before First Reaction

Whether animals are fed to within a few hours of beginning the experiment, or whether they fast for various periods up to 24 hours, seems to make little difference in the survival with large insulin doses. It necessarily makes a difference in the time of onset of hypoglycemia and its symptoms. Some of the irregularities in this interval are explained by the differences in preparation. It is also realized that the active attacks are not an infallible index of the hypoglycemia. Nevertheless there were enough comparisons under controlled conditions to confirm the irregular response of individual animals described by previous writers. In general, the interval before the first symptoms is shortened with increasing dosage but the individual exceptions still occur, and in particular the degree of shortening of the interval is by no means in proportion to the degree of increase of dosage; i.e., sugar consumption and perhaps also glycogenolysis are not very greatly accelerated by the huge doses. Also the shortening of the interval with intravenous insulin administration is much less than might be anticipated.

6. Amount of Glucose Required

The glucose utilization shown in the successive periods evidently maintained a fairly level plateau until the surplus insulin was nearly used up. In the comparison of subcutaneous and intravenous insulin administration, the figures shown for the rats are probably misleading, because most of these animals were overdosed with glucose in the attempt to prevent the high mortality. The rabbits prove conclusively that insulin is less efficient, in the sense that it can be antidoted with much less glucose, when it is given intravenously than when it is given subcutaneously.

The results of these experiments, and also of others in which such large quantities of glucose were given as to prove fatal, reveal no change whatever in the duration of the insulin effect corresponding to any differences in the glucose supply.

7. Duration of Hyperinsulinism

The hours of treatment are counted from the time of the insulin dose to the time of the last glucose injection. In certain instances the disturbance of the time factor by early deaths from large insulin doses must be noticed. In general the most striking point is the trivial increase of rate of glucose consumption, in contrast to the great lengthening of time,* which predominantly governs the amount of glucose used. An argument against insulin-glucose ratios is found in the fact that they thus depend not on an intensity of reaction between the two substances but chiefly upon the length of time insulin happens to be retained in the body. With maximum doses this time may be surprisingly long; e.g., 55 hours in a dog after a single insulin injection, and 100 hours in a rabbit after two injections four hours apart. Theoretically, it would seem possible to extend this time indefinitely, if only the animal could withstand the intoxication from either insulin or glucose.

The inferiority of intravenous as compared with subcutaneous insulin administration, as shown particularly in rabbits (the effect being much shorter, and not particularly more intense while it lasts) warrants two inferences: (*a*) A large part of the intravenous flood of insulin is evidently disposed of in some purely wasteful manner, without benefit as measured by glucose consumption. (*b*) A part of this insulin also is retained in the tissues, as proved by the recurrence of hypoglycemic attacks for the number of hours shown. Therefore, though the method of continuous intravenous infusion may be ideal under the right conditions, if it is used for very large doses it must encounter these same factors of waste and storage, and accordingly proof will be necessary whether it is superior, equal or inferior to the subcutaneous method.

The production of genuine and prolonged hyperinsulinism is readily demonstrated in amputation experiments. For example, if a cat is given an injection of 1000 or 1200 units of insulin near one ankle, and if a mid-thigh amputation is performed 12 to 24 hours later, the general condition and progress and the amount of glucose required remain essentially unchanged. Such animals in fact show a slightly greater insulin effect, as judged by either intensity or duration of hypoglycemia, because of the added element of shock. Such experiments leave no doubt that the essential condition is not a mere delay of absorption, but that a state of true constitutional hyperinsulinism can persist for 48 hours or longer following a single subcutaneous injection.

8. Erythrocyte Counts

To form some idea of the blood concentration, numerous red cell counts were made. Typical results in single individuals of the larger species are shown for various insulin doses in the table. A concentration of the blood

* Likewise with small insulin doses, Zucker and Berg (Am. Jr. Physiol., 1937, cxix, 531–538) found that increased dosage increases the duration rather than the degree of hypoglycemia.

by insulin is established by agreement of most authors (literature by Hill and Howitt). The changes shown in table 4, together with far more numerous examples of marked hydremia in rats not tabulated, seem to be chiefly the result of the large injections of glucose with insulin. The interesting question whether there are any consistent differences in blood concentration with identical glucose injections with and without the large insulin doses was not settled.

9. Final Blood Sugar Figures

The great majority of blood sugar analyses cannot be reproduced. The final figures shown vary chiefly according as they were taken soon or late after a glucose injection. Their only real importance is in showing that animals were not hypoglycemic at death. The earlier unpublished part of each record must be understood as showing likewise that there was no preceding hypoglycemia sufficient to account for the fatality.

It should also be noticed that the time shown in the tables does not represent the true total duration of hyperinsulinism, but only the period of sufficient severity to require glucose injections. Actually, all animals subsequently pass through a stage as illustrated in figure 2, namely a period of perhaps 24 hours following the last glucose injection, characterized by slight general depression and subnormal blood sugar levels, e.g. 50 to 70 mg. With this evidence it is readily proved that a single large subcutaneous injection can produce a state of hyperinsulinism lasting two to three days.

10. Results

In all species, the results of the largest insulin doses were anorexia, depression, weakness, dyspnea, convulsions and death. Hydremia was the rule with glucose injections (not hypertonic). The body temperature commonly became subnormal, especially in rats. Some rabbits and a smaller number of cats showed fever, up to a maximum of 108° F., probably attributable to osmotic effects of the glucose solutions.

In view of the prolongation of time without much increase of intensity of glucose consumption, it might be argued that a large excess of insulin merely lies idle. On the contrary, it appears that (*a*) the large insulin doses produce symptoms of malaise, anorexia, etc. as previously mentioned, increasing as the doses increase, beginning before the hypoglycemia and mostly continuing in spite of glucose injections; (*b*) the increasing severity of this same condition seems to be responsible for slow or sudden death, regardless of the blood sugar if the insulin dose is high enough. At the same time the danger of sudden hypoglycemic death, with a brief convulsion or only one expiratory cry, must be recognized, notwithstanding the apparently slight acceleration of glucose consumption by the large doses. With a few units an animal may have repeated convulsions with weak or unconscious periods between, the available reserves of traces of glycogen, lactic acid, etc.

apparently sufficing as partial antidotes; but doses running into hundreds of units allow no such respite and often demand instantaneous treatment.

11. Epinephrine

Extra stimulation of epinephrine discharge may be suggested in connection with the results of large insulin doses. It has not been feasible to attempt physiological tests or even to investigate possible exhaustion of the adrenal medulla. Since such small amounts as 0.2 to 0.4 gm. of glucose were found to ward off hypoglycemic crises in rabbits, it appeared conceivable that small repeated epinephrine injections might likewise protect against large doses of insulin, or, if glycogen were lacking, that they might reënforce the effect of glucose injections. A few such trials of epinephrine subcutaneously or intraperitoneally failed. A brief reviving effect is obtainable at first, but subsequently the epinephrine appears unable to save life either by itself or by reducing the necessary quantity of glucose.

With reference to the possible suggestion that the toxicity of insulin is due to increased discharge of endogenous epinephrine, the results as far as they could be judged superficially seemed to indicate that the injection of additional epinephrine was helpful rather than harmful.

12. Forced Feeding

As previously mentioned, the advantage of rats with large insulin doses is that they continue to eat while other species lose appetite. Accordingly, trials were made with forced feeding in a species which does not vomit, namely the rabbit. As shown in table 5, it proved actually possible to save life in this way with insulin doses which are fatal when only parenteral glucose injections are used to prevent hypoglycemia. A toxic action of the insulin was still demonstrated by the anorexia itself and by various degrees of weakness. Inhibition of digestion or absorption also seemed to be indicated by the inability to prevent hypoglycemic attacks by stomach feeding alone and the necessity of depending partly upon parenteral glucose injections. Nevertheless there was enough retention of function to prevent any extreme distention or diarrhea and to reduce greatly the amount of glucose needed parenterally.

A careful study was made by parallel experiments in both rabbits and rats, of which details are omitted, concerning a possible specific influence of intestinal digestion or absorption. This touches the well-known questions of antagonism between internal and external secretions of the pancreas, the possible liberation of an anti-insulin hormone during digestion, the special rôle of the liver, etc. These experiments included the administration of equivalent quantities of glucose subcutaneously, intraperitoneally, or by stomach, and pure starch or bread by stomach. It was definitely ascertained that the route of administration or the digestive process has no influence whatever upon either the degree or the duration of the effect, aside from differences in the time of absorption. (Cf. figure 3 in paper no. 1.)

Evidently, the diminished toxicity of insulin when either glucose or starch is fed is due to avoidance of the injury of parenteral glucose injections. The rather difficult question of the respective influence of insulin and glucose can be conveniently studied in rats, though the conditions in other species are similar. If certain rats receive large insulin doses together with a sufficient series of glucose injections to prevent hypoglycemia, while control rats receive the same glucose without insulin, a casual observer can easily distinguish one group from the other, because the insulin animals are humped up, with fur fluffed; they are less lively, have lower temperature, and appear more swollen as if the injected fluid were more slowly absorbed. They may thus die while the controls survive. But if the quantity of injected glucose is sufficiently increased in the controls, the precise appearances of the insulin rats are reproduced and death occurs similarly.

Two possible explanations therefore suggest themselves: (*a*) that the injury from injected glucose is not only physical (osmotic) but also chemical, perhaps through formation of toxic substances as supposed by Fischler, and that this identical intoxication can result from sufficiently large injections of glucose alone or from smaller quantities of glucose under the intensifying action of insulin; (*b*) that the injury from parenterally injected glucose consists solely in osmotic shock, while overdosage of insulin sensitizes the organism to every form of shock. The latter explanation is favored by the lessened injury with glucose feeding, by the easy death of weak animals from insulin, and by the easily demonstrable sensitiveness of insulin-treated animals to surgical and other shock.

A distinction between insulin intoxication and glucose intoxication seems to be afforded also by the autopsy findings. As far as a conclusion can be based upon the few analyses which were possible under the conditions (table 4), animals dying from glucose alone are glycogen-rich while those dying from high insulin dosage even without hypoglycemia are nearly or completely glycogen-free.

Conclusions

1. Parenteral glucose injections produce a beneficial stimulation only with brief administration, and when continued over a long period become harmful or fatal.

2. The tolerance of several species for insulin in conjunction with parenteral glucose injections has been established. Insulin can kill through the carbohydrate metabolism in two ways: (*a*) by hypoglycemia; (*b*) by creating a demand for fatal quantities of glucose.

3. The general conclusions of the preceding paper are confirmed in the experiments with parenteral glucose. The duration of hyperinsulinism is greatly increased with increased dosage, to limits beyond 48 hours for a single subcutaneous injection. On the other hand, the rate of glucose consumption is not increased in proportion to the insulin dose, also the time

required for using up the insulin is not altered by changes in the glucose supply. Glucose-insulin ratios must be regarded as merely imaginary or accidental relationships, because there has never been any evidence of an interaction of glucose and insulin in which the two are mutually and quantitatively consumed.

4. Intravenous injections are much less powerful than subcutaneous injections of insulin, inasmuch as there is no important difference in the intensity of effect as judged by the rate of glucose consumption and the duration of this effect is much shorter; also their toxicity is far less. A large waste of insulin is evident.

5. Large doses of insulin can be antidoted by a series of very small glucose injections, but they cannot be antidoted by a series of epinephrine injections.

6. The most efficient protection is afforded by a combination of enteral and parenteral carbohydrate administration, not because of any specific influence of intestinal digestion or absorption, but only because of avoidance of some of the injury resulting from parenteral injections alone.

7. The excess of insulin above that which produces the maximum effect upon the rate of glucose consumption does not lie idle and ineffective. Absorption is demonstrated by amputation experiments, and by the marked intoxication occurring before the carbohydrate reserves have been seriously depleted or in spite of glucose injections which prevent hypoglycemia. The toxic symptoms resemble those produced by glucose injections alone, but distinctions are apparent; namely, (*a*) in hyperinsulinism the symptoms occur with smaller glucose injections than in the controls; (*b*) according to a few analyses, glycogen is abundant in the controls dying from glucose alone but is nearly or completely absent in hyperinsulinism. The only significance is believed to lie in the fact that hyperinsulinism creates sensitiveness to the osmotic shock of glucose injections and all other forms of shock.

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PSYCHOTHERAPY, WITH SPECIAL REFERENCE TO THE USE OF HYPNOSIS *

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PSYCHOTHERAPY in some form or other is used by every physician, and although the surgeon may use it only occasionally, the internist uses it constantly, even though he may not think of it as such. He may consider psychotherapy as persuasion, readjustment, reëducation, psychoanalysis, hypnosis, suggestion, or even bluff. Every physician admits the use of placebos, and although he may dismiss the case as purely functional, imaginative, hypochondriac, neurotic, or just faking, he usually realizes that the patient wants something done for him and so he gives a prescription, an injection, an electric treatment, or a bottle of medicine with the hope that the patient will have the faith that it will cure him. This faith in the physician and his treatment is highly fundamental, because many patients are treated by the best trained physicians and are never cured, while others get better even without treatment.

In many cases the type of personality with which one has to deal, the stubborn nature of the condition whether physical or mental, or the existing insuperable environmental factors make the treatment, not to mention the cure, almost impossible. In other words, the case may be inoperable. But, if the patients' symptoms are not too fixed and he sincerely coöperates with the physician, then the symptoms may be removed without difficulty, and the distorted personality corrected. It is unfortunate that as a general rule a somatic disorder is categorically diagnosed without regard to the underlying personality, and the treatment instituted is purely physical. On the other hand, if symptoms arise that are obviously psychogenic and are apt to be troublesome, the physician may refer the patient to a specialist to get him off his hands, or he may dismiss him with an uncomplimentary remark and so drive him away from qualified physicians and force him to become the support of some quack or cult. Every physician should remember that properly applied psychotherapy in the form of intelligent management will likely bring about a fair degree of adjustment in the majority of cases, and a true cure is not uncommon.

If the physician finds that the symptoms that he is called to deal with are mostly mental, he should remember that it is unwise for him to tell the patient that there is nothing wrong or that it is all imagination. He may justly resent the one as false and the other as insulting. The fact is, that a functional symptom is just as real as an organic one. Most patients would rather have an organic ailment and be done with it than one which generally gets scant sympathy from the family and indifferent attention

* Read at the New York meeting of the American College of Physicians, April 8, 1938.

from the physician. To insinuate that a patient makes believe, or that his complaints are not real to him, is a serious psychotherapeutic error which will lose the trust and confidence of the patient. He will at once attribute this to the ignorance or lack of understanding of the physician. It is just as grave an error to pat the patient on the back and tell him that he should forget his anxiety, phobia, or compulsion.

The first necessity is for the physician to develop the patient's confidence or establish rapport, by taking the patient, or at least his complaint, very seriously. This is best accomplished by obtaining, as meticulously as possible, a medical and social history and making a very complete and thorough physical examination. No snap diagnosis should be made, and no conjectures should be expressed, but if no physical ailment is found the patient can be repeatedly assured on that score, and the normal anatomy and physiology explained to him. On the other hand, he should be told that a psychic, nervous or mental condition is just as real as a physical one, and that fright, shock, anxiety, or personal conflict may cause nervousness and create definite symptoms. As an example, he can be told that the sweat that comes out on the palms of the hands when a person is frightened is just as real as the sweat that comes out after exercise; or that the diarrhea caused by anxiety is just as real as the diarrhea caused by a dose of salts.

The physician must be careful to use language that will be understood, as most persons, and especially neurotics, have a special capacity to misinterpret what is said to them, and may even conclude that if the physician uses the word mental, he has diagnosed them as "insane." Most people are afraid of going "insane," for that means commitment to a state hospital. On the other hand, although the physician should be understandingly sympathetic, he must never become facetious about the illness or descend to intimacy or levity, but must preserve a sense of dignity and convey the impression that he possesses sound medical knowledge and good insight into the problems of human behavior.

A physician may not realize that when the patient comes to him for help he is willing to bare his very soul if necessary. Every word and action of the physician is seized upon, and without realizing it, the patient develops a confidence that is akin to infatuation or love. If the physician allows any advances or takes any liberties he creates an emotional situation that may lead to grave complications. The so-called "bedside manner" of some physicians should be absolutely discontinued, such as putting an arm around the waist, patting the hand, or as I have observed, even kissing the patient or holding the hand during the conversation. This makes the relationship between the patient and the doctor a personal matter, and will block any constructive psychotherapy. Personal relationships are subject to censorship, and if there is a personal feeling between the patient and the physician, the patient will be reticent about talking about matters that may affect this relationship and yet which need to be brought to light if a readjustment is to be brought about. On the other hand, the physician

should not give the impression that he is a judge, set above the patient, but is a friend who feels what the patient has done is neither good nor bad, moral nor immoral, beautiful nor ugly, decent nor indecent, but the result of circumstances.

The physician should certainly not give the impression that he is a wizard, set apart from the world, who can cause a cure by a wave of a magic wand. Psychotherapy is not a confessional, although a confidential talk may relieve many emotional tensions. It is not a sermon, nor a lecture, nor "psychologizing," nor moralizing, nor "psyching," nor does the physician bewilder the patient with stereotyped symbols, for these may only tend to confuse and befog the problem. Above all, the physician should be a human individual with understanding, self-control and common sense.

It is quite obvious that if some organic defect is found, an attempt should be made to correct it if possible. Unless the organic condition is paramount it is unwise to overemphasize it, for fear that the patient may seize upon some minor or even major physical symptom and continue in his persistent refusal to face the more important problem of getting better. Sometime ago, a young man came into my office very much upset because he had been emphatically told that he needed an appendectomy without delay. In fact the physician who had seen him had told him that he could see in the fluoroscope that the appendix was in very bad condition and about to rupture. The young man wanted to know if he could stand an operation nervously. A thorough physical examination clearly showed that the appendix was not involved, and that the abdominal discomfort was due to intestinal indigestion. The patient was calmed down, put on a corrective diet, and his abdominal pain cleared up without delay. Nevertheless, the seeds of uncertainty had been placed in his mind, and in spite of psychotherapy, he persisted in shopping among the specialists until he found one who would remove the appendix for a consideration. Yet, the personality has not been corrected, and this is the first of a series of operations that undoubtedly the young man will undergo in his attempt to justify his neurotic behavior. The object of psychotherapy, the practice of which literally begins the moment the patient crosses the threshold of the doctor's office, is to influence the problems of personality, while the detailed physical examinations, in addition to giving an understanding of the organic make-up under consideration, in itself becomes a psychotherapeutic measure.

The physical examination may lead one to the conclusion that some operative measure, medication, hypodermic injection, exercise, gymnastics, massage, electricity, baths, rest cure, or what not, may be needed, but suggestion will play a very important part in these procedures. Perhaps the removal of a chronic appendix, or a fibroid, may help to remove the abdominal pain. Certainly foci of infection should be properly treated and complicating organic affections attended to, but one cannot insist too often on the fact that no personality problem was ever cured by mechanical means. Neither surgery, hypodermic or other medication, nor any form of physio-

therapy, will cure a deep-seated phobia, or dispel a paralyzing obsession. Operations, glandular therapy and other medication, are many times curative and necessary, but great numbers of patients have been invalided and their neurotic symptoms made permanently inaccessible by the unwise application of these methods.

Because of high-pressure salesmanship by drug firms, and lack of understanding on the part of the physicians, narcotics and hypnotics are indiscriminately dispensed or prescribed. In general it may be said that the less medication and the more psychotherapy, the better, although with inaccessible patients often all one can do is to prescribe some placebo. But even so, the effectiveness of most prescriptions is in direct proportion to the amount of suggestion they embody.

There is no objection to a patient taking a trip, a brief sojourn at a health resort, hospital, sanatorium, or spa, but obviously the virtue of such treatment resides in the efficacy of temporary removal from the aggravating environment. Since personality problems are rooted in inner and outer conflicts, and the patient takes the former with him, and must return to the latter, it is highly probable that no permanent benefit will be derived from temporary or even prolonged sojourn away from home.

Physicians are frequently confronted with the results of pilgrimages to places where faith or miracle cures are performed, and there is no doubt that isolated and spectacular cases of religious hysterics with outspoken conversion phenomena have been helped. But these cases can all be explained by the effects of suggestion, and most other cases go unhelped.

It is necessary to remember that many environmental factors are beyond the ability of either the patient or the physician to cope with, and yet it is obvious that these factors may be the cause of symptoms, although the genesis of functional symptoms is not one of logic or intelligence. The subjective, emotionally tinged, unconscious, is at the back of these symptoms, and besides the need for adjusting the personality to the environment, it is well to bear in mind that mentally created symptoms are in themselves a compromise attempt at adjustment. These symptoms may have been unconsciously grafted on to the personality pattern, during childhood or later years, through the method of suggestion.

Without realizing the source of these symptoms, the physician may attempt to reason them away through persuasion. Persuasion denotes an appeal to moral sentiments. The attempt is consciously to resolve conflicts and reintegrate the personality. Obviously this implies an intellectualistic concept of the etiology of neuroses, while actually, functional symptoms are rooted in deep-seated unconscious conflict, and no amount of reason or persuasion can dissipate them permanently. If the symptoms disappear as a result of this procedure, then suggestion should be given the credit.

It is possible that by painstaking reconditioning, symptoms may be changed, and the personality reëducated, but even with this method, suggestion plays a major rôle.

During the past few years there has been much discussion about treatment by psychoanalysis, and some therapists would lead us to the conclusion that psychoanalysis is the best, if not the only method of mental treatment, while other physicians who have but a smattering knowledge of the technic, condemn this method without reservation. Certainly it is not the only method of treatment. Every method has its advantages, and it is well to remember that not every patient lends himself to psychoanalysis; most physicians lack the special technical skill and training; and the method is so individualistic and time-consuming, that it cannot very effectively be employed in most cases. Perhaps the first critera for the use of psychoanalysis is to gain insight into one's own character before trying to unravel the patient's problems. This may mean that the physician may need to undergo an analysis before attempting to analyze some one else. One thing is certain: most individuals cannot learn psychoanalysis from books and lectures alone. Above all, if the physician would do psychoanalysis he should have good sense, native understanding, and ethical conduct.

There are physicians who are apparently well trained in the technic of psychoanalysis, but they are slaves to theory, and the technic masters them, and they can see nothing beyond the horizon of sexuality.

As stated before, not all patients can be analyzed. The patient must be fairly intelligent, and sufficiently educated to understand the method and purpose of analysis. He must want to get well, and be prepared to perhaps change his whole outlook on life. In any case, it is expensive in time, energy, and money, for an analysis takes at least a year, and an hour daily may have to be spent for several months before any headway can be noted.

In a few words, the object of the physician in analyzing a patient is to direct the patient in the analysis of himself, and to thus make him aware of the significance of unconscious impulses. By such direction, he gains insight into the meaning of the symptoms which he wishes to be rid of. The physician does not even tell the patient what to do or say, nor does he lay down any rules, except possibly a few general ones. After all the unconscious material has bubbled over, and the patient's mind has literally undergone a catharsis, then the physician leads his patient into a synthesis and reintegration of his personality.

If the patient has been successfully analyzed, he is freed from unconscious conflict, and is capable of making an adjustment to difficult situations or at least meeting them in an objective way.

But not all analyses end in this theoretically ideal manner, because the character and personality may be too ingrained to permit of radical transformation. If a patient does not show definite progress for the better within six months or give promise of a cure within a year, the analysis should be discontinued, and certainly there is nothing to be gained by repeated analysis.

The psychoanalytic technic has been frequently changed within past years, and there is no indication that it has yet become stabilized. The

Freudian psychoanalysts are inclined to claim that no further supervision or guidance is necessary after the completion of an analysis, while the Jungian psychoanalysts state that the analysis is never completed and that there are no limits to personality development. It is obvious to every physician that no one ever attains such a degree of excellence that no further aid from others is necessary. A sickness may be ameliorated or cured, but there is no telling when there will be a " reinfection " or relapse. Although psychoanalysis has contributed more to our knowledge of personality forces than any other method of investigation, as a form of psychotherapy it is still in an experimental stage. Perhaps unknowingly, even before the announcements of Freud in 1895, physicians made practical application of the principles of psychoanalysis, and they undoubtedly will continue to do so as far as their experience and judgment permit.

Suggestion is the oldest and most widely used method of psychotherapy, and history is replete with examples of miraculous cures based on faith in some inanimate or animate object. It is impossible to eliminate suggestion from any form of treatment. Patients wish to be relieved of their suffering, and every physician knows that much of the medicinal and surgical treatment owes its beneficial effect to the element of suggestion. The tradition of medical and surgical procedures is so firmly established that even the most enlightened patient feels that something is lacking when treatment is carried out without " a laying on of hands."

Suggestion is associated with the subconscious mind, and as a great part of our life is subconscious, suggestion is at work in innumerable ways at almost every moment of the day. We are constantly receiving suggestions many of which may lie hidden and apparently lost in the subconscious mind and yet be hourly and daily shaping our characters. Perhaps these suggestions were first planted during childhood, for the human being is at no time more suggestible than during childhood. So indelibly are the impressions of childhood stamped upon the individual that they influence all the future life for good or evil to an extent that is astounding. Psychiatrists who have attempted to reëducate a warped or twisted character, are impressed constantly with the necessity for seeking the cause of the warp or twist in the half-forgotten experiences and memories of childhood.

Most people are slaves to their unconscious, the product of ancestral times and early habit patterns, and they constantly accept many facts without wonder and without any sensation of witnessing the miraculous, simply because these facts have become familiar. That shame or pleasure should cause a flow of blood to the cheeks, is so familiar a phenomenon that it causes no wonder. But if the memory of some unpleasant experience should cause an allergic-like skin reaction, the physician seems in a quandry. Every physician is familiar with the fact that worrying thoughts, or fright, have the power to upset the normal peristalsis of the stomach and intestines, but they may not realize that the secretions are altered, and indigestion, constipation, diarrhea, or colitis may be caused by the emotions.

Suggestions are constantly pouring in upon us from the sights we see, the sounds we hear, the people we associate with, the work we do, the books we read, the sermons or lectures we hear, the advertisements we observe, the radio announcements to which we listen, the plays, the movies, and the concerts to which we go. Suggestions are in fact influencing us the whole day long, and half the night. Some of them are accepted and acted upon, while others are resisted by counter-suggestion from higher authority. Many are apparently forgotten, but nevertheless are stored for all eternity in the subconscious mind, and perhaps continue to influence our lives momentously. There is ample evidence to show that human beings are greatly influenced by the subconscious memories which in one way or other have been transmitted from centuries of ancestors. Humans fear the dark because of the subconscious memory of prehistoric days when the fall of night meant danger.

It is thus evident that not all suggestion comes from outside. The person may suggest ideas to himself. Some people live in constant apprehension, in constant expectation of developing some bodily ailment, and so are ready at any moment to interpret trifling symptoms as having a grave significance. Should they have slight indigestion and "heart burn," they are convinced by self-suggestion that they have heart disease, and promptly suffer palpitation and breathlessness. Fortunately in most cases such symptoms vanish with examination and assurance by the physician. In other cases, however, matters are made worse by the statement of the unscrupulous or ignorant physician.

If an article of diet once upsets the digestion, the patient is too apt, prompted by strong self-suggestion, to feel sick or be sick every time the article is served or even mentioned. There may be an allergy, but more often an unconscious fear. If the patient is raised to believe that fresh air is the mainstay of life, then he will suffer agonies, often quite disproportionate to the atmosphere of the room. Then there are the persons prepared to go on a voyage and to be sick according to the usual custom, and who become sick even if the vessel is unavoidably delayed. Or, the woman who has been told that nausea and vomiting are expected during pregnancy, so hyperemesis gravidarum develops. Perhaps a mother or grandmother suffered from dysmenorrhea, and the girl was told she could expect to be miserable when she menstruated for all women had the "curse," and so painful menstruation continued the tradition in the family. It was also a family trait to be constipated, to have sick headaches, or bilious attacks, and the newspapers and radio intensified the belief, and so the delusion was carried on from generation to generation.

But just as harmful suggestions may cause havoc in the human body, so helpful suggestions may bring good results. Fortunately hypnotism, which will be discussed later, though invaluable for some obstinate cases, is not the only way in which a helpful suggestion can affect the subconscious. Take, for example, happiness; sudden and unexpected happiness, under the

various forms in which it comes, is a most potent health-giving factor. When all medical remedies have failed to act, happiness has the power of making an immediate and convincing appeal to the subconscious self, and in the space of a few days the external signs of ill-health are gone, the eyes bright, the complexion clear, digestion normal, sleeplessness vanished, and health is restored as if by miracle.

As a rule, treatment by suggestion is given while the patient is awake, but in carefully selected cases, it may be best employed during sleep. When suggestions are thus given, the patient is put into a state of hypnosis. In this state, conscious resistance is reduced to a minimum, and the patient is put in a condition of heightened suggestibility. Since the conscious mind is in abeyance, suggestions are accepted without criticism by the subconscious mind and are put into action.

In an earlier paper,[16] I brought out the fact that it was unfortunate that hypnotism suffered the fate of other methods of therapy which have become associated with charlatanism and which have been hailed with undue enthusiasm. It fell into disrepute with physicians because, unlike psychoanalysis, it deals largely with symptoms rather than with causes. On the other hand, these arguments are hardly justified when it is realized that many standard methods of therapy are used by the charlatans, and physicians seldom know all the causes of an illness before attempting to treat it.

Hypnosis offers an approach to many psychogenic difficulties since it allows the physician to directly influence the subconscious. The dissociation brought about may serve as a gateway past resistances and allows indirect approaches to problems which otherwise could not be attacked. As is well known, one of the greatest obstacles in psychotherapy is to get the patient to consciously accept therapeutic suggestions. Under hypnosis it is possible to implant therapeutic ideas upon the " subconscious " and to have them take effect when endless numbers of suggestions given in the waking state would be given no heed or even actively resisted. Under hypnosis the patient accepts therapeutic suggestions, and acts upon them without conscious awareness and without building up defense reactions. Also, under hypnosis former dissociated experiences and amnesic material can be rendered available for re-association and reorganization. These statements sound overly enthusiastic, but it is not wished to imply that hypnosis offers a panacea. On the other hand, within limitations it is a valuable addition to the armamentarium of the properly trained physician.

The application of hypnosis requires no unusual personality or " strong will " on the part of the practitioner nor " weak will " or feeble intellect on the part of the patient. Any person willing to learn the psychological principles involved can perform hypnosis, but like psychoanalysis or any of the specialties, the practitioner should be duly qualified. It should be understood that the use of hypnosis is essentially a matter of technic, a technic of convincing and persuasive suggestion similar to that utilized every day in advertising and salesmanship. Just as almost anyone may be a hypnotist,

so practically anyone may be a subject. The best subjects are highly intelligent patients with good powers of concentration. There apparently is no difference between the sexes, although the younger adults or adolescents are more receptive, and extroverts are more responsive than introverts.

Like any form of psychotherapy, the results of hypnosis are individually limited, and vary in degree and variety with every subject, depending, of course, upon the innate endowment of the patient. Furthermore, all phenomena do not necessarily occur in every subject, but only manifest themselves as a rule. Some patients fail to show this or that particular characteristic response to hypnosis.

The mechanism of normal sleep and that of hypnosis are the same. Normal sleep, like hypnosis, is a condition of dissociation. In fact, spontaneous somnambulism produced in normal sleep can be transformed into hypnosis, and this in its turn can be terminated in normal awakening or normal sleep. The physician can not infrequently influence by suggestion a normally sleeping person and transport him into hypnosis without awakening him. It is still easier, in the reverse direction, to transform hypnosis into ordinary sleep by suggestion.

Physiologists have done a great deal of work with sleep in an attempt to explain its mechanism. There is no doubt that through the process of association the vasomotor reflex centers can be stimulated. Also the reflex centers for the closure of the orbicularis oculi muscle may be stimulated, and thus call forth the neurodynamic processes which bring about sleep. This mechanism may also be brought about by exhaustion or drug action on the cortex. Stimulation of the vasomotor centers brings about an increasing anemia of the brain, with its accompanying dullness, and sleep. When this condition progresses sufficiently then the person loses touch with reality and dissociation takes place. Dissociation is when the normal constellations are deflected from their usual distribution and activity.

Hypnotic suggestion is a method of invading the associated dynamics of the brain. It may be used to dissociate that which was associated, or to associate that which was not associated before. From what has been said before it is evident that at first its chief invasion is an inhibitory one, as it dissociates the associated automatisms of the brain. The dissociated dynamics of the brain of the person under hypnosis are in a condition of receptivity or hypotaxis, as compared with the well-concentrated and associated dynamics of the physician, which press suggestions upon the patient's subconscious by way of the special sense organs. The patient becomes plastically moldable, and is compelled to adapt himself more or less irresistibly to the physician's suggestions. The cause of this apparent subordination does not lie so much in the strength of the physician as in the patient's feeling and conviction that he is being subjected to a dynamic influence. All persons are in a condition of hypotaxis, or dissociation during normal sleep, and confuse dream thoughts with actual occurrences. It is for this reason that sleep is advantageous for the application of suggestion.

During sleep even the most "powerful" brain or well integrated personality obeys the suggestion of an otherwise less "powerful" brain, which is awake and in an associated condition.

The physician who wishes to use hypnosis must know how to convince his patients that he is capable of doing so, and he must be able to more or less induce an enthusiasm for this form of treatment. Thus the practitioner must either be convinced himself, or, failing this, possess a dramatic personality, in order to convince others. Everything which fills a person with enthusiasm gains control over his brain activity, easily conquers all the contrary impressions, and leads the person into receptivity. Therefore, the hypnotizability of a person increases with his enthusiasm and with his confidence, as well as with the enthusiasm and former success of the practitioner. And, vice versa, it sinks with the abatement of the enthusiasm, with mistrust, and with failures. On the other hand, many other individual factors as mentioned before also assist in the application of hypnosis, such as individual plasticity and intensity of the impressionability, exhaustion, sleep capability, etc.

As the patient goes into hypnotic sleep, the field of consciousness narrows and external stimuli, except those given by the practitioner, lose their significance. Ultimately the subject loses contact with the external world except for the operator. Essentially, the "conscious" loses control, while the "subconscious" is left in rapport with the physician. This rapport, which is one of the important phenomena of hypnosis, may be defined as a state of harmony between the patient and the physician, with a dependence of the former upon the latter for motivating and guiding stimuli, and is similar to the "transference" of the psychoanalytic situation. It enables the practitioner to remain in full contact with his patient while to the rest of the world the hypnotized person remains unresponsive. Nevertheless, under hypnosis this rapport may be transferred by the command of the physician to any designated person.

As has been brought out, hypnosis comes as a result of coöperation. Without full coöperation between the patient and the practitioner there can be no hypnosis. Unwillingness to be hypnotized, admitted or concealed, prevents this essential coöperation and consequently hypnotic sleep does not and cannot occur.

As long as the aforementioned essential principles are observed, the exact technic of inducing hypnosis is of secondary importance, but the physician should vary the details of his technic to fit the individual patient, and it is unwise for the physician to say that he will or can hypnotize anyone until he has made a trial. The fact that a previous hypnotist was unsuccessful is not necessarily proof that he will fail. Success is not precluded by the patient being restless or showing uncontrolled movements. The patient's consent should first be obtained and, in some cases, this should be in writing. The physician should disregard a statement such as "I had such a good night that I do not feel sleepy." Often on the first occasion

an audience may distract the patient as well as the physician but it is hazardous to be alone with a woman, so a witness should be present. Before starting the hypnosis, the practitioner should write down the items he wishes to find out or suggest, and write down also the results directly they occur, as it may be impossible to remember the phase to which each of them belongs. If he plans to suggest disappearance of sensory anomalies he should first know accurately the patient's reactions to stimuli.

The first attempt to induce hypnosis may produce either a slow or a rapid sleep, but afterwards sleep as a rule is rapid. Occasionally after a rapid induction the patient resists sleep subsequently and the second induction is slow. Although the patient's coöperation, as well as his consent, is necessary at the outset, once the patient has been hypnotized the physician will thereafter succeed in placing the patient under hypnotic control if proper technic is followed.

In most cases the patient should be asked to sit in an easy chair or lie down, and relax his muscles. Many people find it difficult to relax, even though their attention has been immobilized. He should not be told to think of nothing at all, for this is impossible. It is well to ask him to imagine himself somewhere where the scene is familiar, pleasant, and neutral, such as a park or in bed at home, and pretend to feel drowsy. He may be able to help this simulation by emphasizing his expirations. He should pay no attention to the physician at the beginning of the procedure; for illustration, the ease of attention in church can be advised. The patient is then told that he will be instructed when he is to start listening, for this is not required until after dissociation has occurred. The patient is then told to look at the physician and at once is told to transfer his gaze to some object which is held in front of his eyes, such as the index finger and thumb, a pencil, or an examining light. He is told to continue to stare at it, if possible without blinking. As a rule a bright object is best, but the object is immaterial. During this stage the physician should suggest ocular fatigue, speaking in a monotone but confidently. It is seldom necessary to make any passes and many patients dislike it, although it may be useful in obtaining relaxation. The physician should bring the object nearer and nearer to the patient's eyes and tell him that he can no longer keep them open. When the lids have closed he is told that he is unable to open them of his own accord. If dissociation takes place the faculties are at once reduced but they can be restored to full activity at a word, without waking the patient. There are several features in this technic which resemble those of putting a child to natural sleep.

In general, staring into the patient's eyes is inadvisable, as the effect produced by eye on eye is considerable and may be unpleasant. It may impress the patient too much, although in selected cases this may be desirable.

At the moment of dissociation the eyes rotate upwards and the expression alters. The patient may become restless for a few moments. Rota-

tion occurs the instant before the lids close, and cannot be voluntarily controlled. Sometimes a patient will appear to make a great effort to remain associated, opening his eyes at once and relaxing his rotation; he may repeat this behavior several times. A few words by the physician makes dissociation complete. Rotation takes place in the natural movements of blinking and also in natural sleep, although it is absent in general anesthesia. It does not always persist during sleep. In blinking it occurs simultaneously with the dropping of the lids and is thus unobserved. The individual himself is unaware of it.

If after the hypnosis the lids are opened the rotated eyes are seen not to be squinting, as is the case in natural sleep. The pupils usually come down and are directed forwards as the lids are separated, and then they may wander laterally, with squint.

Where there is some difficulty in getting the patient to relax, he may be given a hypnotic drug to assist in the induction of controlled hypnosis. The barbital compounds, bromides and paraldehyde may be used, but the essential principles as above outlined also have to be followed. If these drugs are used, they should only be used for the initial inductions, as in many cases the results are unsatisfactory because the chemical effects frequently interfere with manifestations of the hypnotic phenomena. It is well to remember that drugs should not be used in ambulatory patients, as the patient should be allowed to sleep off the chemical effect of the drug before awakening, otherwise the "hang-over" will act as an auto-suggestion. Also, the routine of awakening the patient by suggestion cannot usually be followed if drugs are used to induce hypnosis.

When undergoing hypnosis the patient first begins to be drowsy and to feel sleepy; and, if he wishes, he can at this stage stop the hypnosis. This stage is known as somnolence, and it is during this stage that external stimuli are most liable to distract the patient's attention. His confidence may thus give way and he awakes himself, and refuses to follow further suggestions. In spite of the fact he can resist suggestions, he can only do so with a certain amount of difficulty.

As the patient goes deeper into hypnosis he concentrates more and more on what the physician is saying to him, external stimuli have less and less effect, and the patient finds himself doing automatically what he is told to do. In this stage, known as hypotaxis, the patient's eyes are closed and he cannot open them except on the express order of the physician. In fact nothing can be done except it is ordered, and then it must be done. The patient may describe his feelings as if his mind were separated from his body, and as if he were able to watch his body behave as though it had nothing to do with him. He may recall this dissociated experience as if he were recalling a dream.

If the patient goes into deepest hypnosis, known as somnambulism, he has given himself up completely to the physician. He will walk about and perform all kinds of actions, and there will be complete amnesia, if the

practitioner orders him to forget or if the patient himself believes he will not remember what has happened. On the other hand, many patients are apprehensive about this point, and they must be reassured that they will remember everything that happens while they are under hypnosis, if they so wish. However deep the hypnosis, the patient will remember everything if he is told to do so.

Most patients can be put deeply under hypnosis at the first session, although some may require three or four sittings before the deeper stages of hypnosis are reached. The patient needs to be reassured that because he did not go deeply under the first time is no reason that he can not be hypnotized.

Once a patient has been successfully induced into hypnosis he can be conditioned to become dissociated instantly and apparently deeply on future occasions, in response to any signal which has been selected. This may be a stare, a click of the fingers, a written word or a word spoken in a whisper. It is immaterial whether the patient is alone or in a crowd, but he must understand the significance of the signal. He can also be conditioned to hypnosis by radio or telephone. Reassociation in response to a signal occurs equally rapidly and, once again, dissociation. Both phases can be produced without any coincident eye change or alteration of the features so that it may be impossible for an observer, even with the closest scrutiny, to identify the patient's condition.

If the physician wishes the patient to reënter his influence by spoken word, sign, letter, telephone, telegraph, or radio, he can usually ensure it even at a distance, by giving instructions either before, during, or after hypnosis. If reëntry is not desired he should counter order it before he wakes the patient. If this preventative is not administered, any of the three stages of hypnosis may occur spontaneously and may be mistaken for absentmindedness, spontaneous trance, the loss of identity as in hysteroid epilepsy, or something more serious.

As brought out in my former paper [16] it is within the realm of possibility that some of the compulsion neuroses and the hallucinations of the psychoses may be explained by this same mental miscarriage. It has been shown that thought processes passing through the brain can be detected and even measured by electric oscillations. Also the temperature of the body can be raised and vasomotor changes effected by passing radio currents through the body. It is not far-fetched to assume that sensitized persons suffering from certain atomic changes in their tissues may thus tune their special senses or brain cells into a specific radio frequency and so become sensitive to suggestions that are known to be always passing through the ether, and which are normally detected by means of radio receivers or will be detected when proper instruments are devised. These "sick" persons are in various degrees of dissociation and hypersuggestibility and so may misinterpret these stimuli. On the other hand, these "radio" suggestions planted in the brain of the patient may set up auto-

suggestion and so lead to compulsions, just as suggestions given to a patient under hypnosis may direct his actions after he awakens.

A patient may pretend to be hypnotized or may deny afterwards that he was under hypnosis. After hypnosis there is no yawning, and no laughter, although the patient will laugh if he is told to behave naturally. When he is told to walk about and do things his eyes are as a rule directed forwards and the lids almost closed. He opens his eyes directly he is told. Some patients maintain the upward rotation as they walk about and, being unable to see where they are going, bump against furniture; it is notable, however, that they do not grope their way as a blind man does and as a man might if he were pretending to be hypnotized. The persistence of rotation and eye closing may be due to the physician's insistence on "You cannot open your eyes," during the induction. Rotation sometimes persists with the lids open, but ceases when the patient is told to look forwards. Flickering of the lids, due to restless eyes, indicates that the patient is not under hypnosis. It might be expected that the patient at the moment of dissociation would drop something which had been put into his hands, but he does not let go unless he is told to do so. The physician's influence over the patient's conduct has no special value for differential diagnosis for, if the patient is pretending he will do most unexpected things if he is told. A note should be made of what is said to him and his replies, so that he may be tested later. If he has been under deep hypnosis, and has not been instructed to remember what he was told while asleep, he will recall nothing, but if he has been pretending he may repeat the conversation out of ignorance.

The physician may believe that the patient is hypnotized whereas he has merely fallen asleep. Although a patient may become hypnotized during the procedure it does not follow that he is under the physician's influence; it may be found that he does not talk to the physician and that the physician cannot rouse him. This condition may be due to his reëntry into the influence of a previous hypnotist, a state which the procedure has suggested.

The failure of suggestions to be followed is no evidence that hypnosis has failed. In seeking to demonstrate the influence on a patient's muscular power it is well to remember that he may show very great power by an effort of will, although it is in hypnosis that the extremes of flaccidity will be manifested. As regards the sensory side, a patient awake may bear a great deal of pain without showing it, if he is so minded, and every physician has seen profound alterations in sensibility, involving even the cornea.

There is no reliable criterion of depth of hypnosis, but perhaps the distance of memory recall and the subject's readiness, after being awakened, spontaneously to reënter the physician's influence may be so regarded. A patient has no better knowledge of the duration of his hypnotic sleep than he has of normal sleep. Failure to obey is apparently no criterion of the depth of hypnosis, nor is difficulty in waking the patient; but the physician should have no difficulty along this line, provided the patient slept for him

and remained under his influence. Whatever the apparent depth of the hypnosis, a patient may wake spontaneously even in the face of a continued order not to do so, and this is particularly liable to occur if the eyes are investigated or if a suggestion is unconvincing or unacceptable.

On waking, the patient may rub his eyes and seem dazed, but he does not yawn. If he complains of headache it is slight and transient. Some patients appear to have no knowledge whether sleep has been artificial or natural.

If during the hypnosis the physician had arranged for a substitute to wake the patient he can leave the patient without feeling anxiety, but if this has not been done the patient will either remain under hypnosis until he awakens spontaneously, or he will transfer himself into natural sleep from which he will awaken in due course or from which he can be aroused by anyone. It is well to remember that a general anesthetic may cause the dissociation to give way, or the physician can give a demand to awake over the telephone and thus awaken the patient.

Failure to put a person under hypnosis is fairly common even though success can ultimately be attained, and the reason lies with the patient rather than the practitioner. He may be over-interested or distracted; a tight garment or a distended bladder is enough to prevent hypnosis at the first trial. The patient may fall asleep or may sleep naturally after first passing through a brief stage of hypnotic sleep. There may be coöperation and yet sleep may have been forbidden by a previous hypnotist, either when the patient was awake or under hypnosis. The patient may protest that he is coöperating, whereas he is strongly resisting, and this may be due to an anxiety about the procedure in general or to a fear of what he may be caused to do or say as a result of hypnotic suggestion.

If the patient is a receptive individual, and the physician has been careful to properly apply the technic, there is no telling what symptoms can be removed by hypnotic suggestion. Care of course should be taken not to suggest a movement of an arm or leg that is organically paralyzed, or to try to bring back the memory of an amnesia victim in whom there is extensive brain destruction. But, the experienced individual is often surprised by the dramatic results that unexpectedly occur in cases that he may consider beyond help. A long standing paralysis that has resisted all other forms of treatment, may immediately recover under hypnosis. A case of amnesia may be awakened into reality. An insomnia case may sleep like a baby. And even in cases of obvious organic pain, such as childbirth, amputation or laparotomy, the patient may go through the ordeal without flinching, and in any case show better response to the anesthetic, if hypnotic suggestion is used.

Summary and Conclusions

1. Psychotherapy begins the moment the patient enters the physician's office, and the patient's confidence should be established by a careful medical and social history, followed by a thorough physical examination.

2. Placebos are justified, but their effectiveness is in direct proportion to the amount of suggestion they embody.

3. Psychoanalysis may be successful in selected cases.

4. Suggestion is continually affecting the subconscious mind, and may influence the person for good or bad.

5. Hypnosis has a definite place in psychotherapy, as it is not a mysterious art, but a scientific technic.

6. Under hypnosis the patient has increased suggestibility, and any suggestion not objectionable to the subject will be accepted and acted upon. Thus hypnosis may be used to overcome many functional symptoms, and to supplement other forms of psychotherapy.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1937

(Fifth Rheumatism Review) *

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In Two Parts

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Part II

HYPERTROPHIC (SENESCENT, DEGENERATIVE, OSTEO-) ARTHRITIS

It has been reliably reported that practically every person aged 50 years or more can be shown to have hypertrophic arthritis but that only about 5 per cent have symptoms of it. At that rate, in 1935 there were at least 23,726,900 Americans with hypertrophic arthritis, of whom presumably about 1,200,000 had symptoms. But in spite of its great incidence this

* This Fifth Rheumatism Review was prepared by the Editorial Committee (Dr. Hench, Chairman) of the American Rheumatism Association. The editorial comments express the opinion of the Editorial Committee, the authors of the Review, not that of the Association.

Received for publication November 28, 1938.

disease remains a neglected stepchild in the family of rheumatism. Although hundreds of reports on rheumatic fever, on gonorrheal arthritis and on atrophic arthritis appear annually, few appear in which hypertrophic arthritis is the sole or chief topic; less than six appeared during the year reviewed. Certainly a disease so prevalent and distressing, even if not as tragic as atrophic arthritis, deserves more serious consideration than to be used almost exclusively as a source of control material by those studying the chemical, immunologic or roentgenologic reactions in atrophic arthritis. A comparison of three current reports (Buckley; O'Reilly; Ray) fully discloses the incompleteness of knowledge of the disease, not only of its etiology but even of its clinical and roentgenologic picture. For example, most writers regard Heberden's nodes as the commonest expression of hypertrophic arthritis; one writer,[511] however, stated that Heberden's nodes practically never occur in (what he calls) osteo-arthritis and that their pathologic characteristics have nothing in common with those of osteo-arthritis. According to one physician [503] in osteo-arthritis terminal and also carpometacarpal or metacarpophalangeal joints may be affected; according to another,[84] terminal phalangeal joints are affected before proximal (interphalangeal) joints but the wrists and metacarpophalangeal joints "invariably escape"; according to a third writer,[511] hands are never affected in "osteo-arthritis." According to Buckley, spinal osteophytes are manifestations of osteo-arthritis; according to O'Reilly, simple osteophytic lipping does not, per se, constitute osteo-arthritis.

Definition. With such ideas in conflict, obviously there is as yet no final agreement as to the proper clinical and roentgenologic definitions of hypertrophic (osteo-) arthritis. Writers are finding it increasingly necessary to qualify the terms "hypertrophic" arthritis and "osteo-arthritis." We have discussed in previous Reviews the importance of realizing that the clinical picture and the roentgenologic picture of hypertrophic arthritis are not necessarily synonymous and that a roentgenologic pattern of bone hypertrophy (hypertrophic arthritis in the roentgenographic sense) is a feature which may be present at certain phases and in certain joints (weight-bearing ones especially) in many types of arthritis which are clinically entirely different (traumatic, gonorrheal, gouty, psoriatic, even atrophic arthritis). Therefore hypertrophic arthritis, roentgenologically speaking, is by no means always the equivalent of hypertrophic arthritis, clinically speaking. To make these distinctions more clear some believe that the clinical syndrome should be named, "primary hypertrophic (or osteo-) arthritis" to distinguish it from the several roentgenographic patterns of "secondary hypertrophic arthritis" seen during the course of a number of articular diseases.

[One of us, P. S. H., frequently has found it clarifying to combine etiologic (?) and roentgenographic terms, and to speak of "senescent hypertrophic arthritis" as distinguished from "gouty hypertrophic arthritis" or "traumatic hypertrophic arthritis," and so on. But it must be realized that, as the disease progresses roentgeno-

graphically, what is senescent hypertrophic arthritis or gouty hypertrophic arthritis one year may, as time passes, be more correctly described later as "senescent destructive arthritis" or "gouty destructive arthritis."—Ed.]

In line with this conception, Race and Ray noted that "secondary osteo-arthritis" may be the sequelae of rheumatoid arthritis in weight-bearing joints, of gout and of certain diseases in which marked decalcification occurs, such as osteitis deformans. O'Reilly defined his conception of (primary) osteo-arthritis, which will be discussed later, and noted that in certain joints never affected by primary osteo-arthritis, osteo-arthritic changes (i.e., secondary osteo-arthritis) occasionally occur secondary to known causes (fracture, chronic trauma, rheumatoid arthritis, and so on) but "they are not osteoarthritis." Thus, the simple lipping such as one often sees in a bunion joint of the great toe is not true osteo-arthritis, according to O'Reilly, but a physiologic response to constant trauma.

[Would it not have been clearer had he stated it thus: The lipping often seen in the great toe is not evidence of senescent (or primary) hypertrophic arthritis but of a physiologic response to trauma; i.e., traumatic hypertrophic arthritis (or, to use the English synonym, secondary traumatic osteo-arthritis)?—Ed.]

Incidence. Of 9833 patients admitted in three years to the Devonshire Hospital, Buxton, 1069 (11 per cent) were classified by O'Reilly as having true osteo-arthritis. Because the disease begins and may progress insidiously before producing symptoms, statistics on age incidence refer to the onset, not of the disease but of symptoms. Among 94 patients, O'Reilly noted the following age incidence: four cases (4 per cent) between 30 and 40 years; 21 (22 per cent), between 40 and 50 years; 42 (46 per cent), between 50 and 60 years; 22 (23 per cent), between 60 and 70 years, and five (5 per cent), between 70 and 80 years. As Miller noted, one occasionally sees typical hypertrophic arthritis, with Heberden's nodes, affecting patients considerably less than 40 years of age.

Ray noted the usual predilection of the disease for weight-bearing joints and for those used in certain occupations but O'Reilly noted no special occupational incidence in 100 cases.

Clinical Data. The orthodox clinical picture was again described.[84, 473, 563] Miller noted that prodromal symptoms of hypertrophic arthritis are not so numerous or so striking as those of atrophic arthritis but "may include headache, malaise, impaired digestion, sluggishness of bowels and a disturbance of metabolism."

[We are not inclined to agree with this statement. These symptoms are common to persons of this age group whether they complain of hypertrophic arthritis or not; we have not noted these prodromes with sufficient frequency or consistency to consider them to be related to the disease.—Ed.]

O'Reilly and Buckley emphasized an insufficiently recognized point: Hypertrophic arthritis is generally associated with considerable "senescent fibrositis" or "fibrositis of the degenerative type." Subcutaneous nodules

are rarely or never seen in hypertrophic arthritis, according to Miller. Already noted were differences of opinion as to the "articular geography" of true hypertrophic arthritis. According to Ray, the thumb base is commonly affected and either carpometacarpal or metacarpophalangeal articulations may be affected. According to Buckley, terminal finger joints are affected before interphalangeal joints, but metacarpophalangeal and wrist joints "invariably escape" in true or primary osteo-arthritis.

[From the micropathologic standpoint, practically every joint of persons more than 50 or 60 years of age is affected with at least the first stages of hypertrophic arthritis, i.e., with degenerative fibrillation of cartilage, precursor of later hypertrophic bone reactions. Roentgenographically also, certain joints of persons more than 50 years old (e.g., those of the spine) are almost always affected. But although most of his joints might be shown microscopically to be affected with degenerative changes (precursors of hypertrophic arthritis) the elderly patient generally will note symptoms only in certain joints and practically "never" in others. Thus, the disease clinically affects knees, cervical and lumbar spine and terminal phalangeal joints commonly; sacro-iliacs, interphalangeal joints and hip less commonly; metacarpophalangeal joints and wrists rarely if ever.—Ed.]

In spite of their great frequency there is strangely no common agreement as to the anatomic nature of Heberden's nodes. Heberden's own description was so meager that it has permitted to arise many diverse clinical, pathologic and roentgenologic definitions. Current papers reveal this confusion. According to Buckley, degenerative fibrositis "may appear as Heberden's nodes which gradually become ossified and constitute one form of osteo-arthritis differing from other forms in that (still according to Buckley) the articular cartilage is unaffected. These nodes appear at the bases of the terminal phalanges and are at the beginning cystic in character, filled with a gelatinous substance." Ray's interpretation follows: osteophytic outgrowths often affect terminal phalangeal joints but "osteophytic outgrowths are not quite the same as Heberden's nodes which spring from epiphyseal ends of the bone. One would say that an osteophytic outgrowth that was causing distortion was not a Heberden's node because the latter do not give rise to any displacement of joint surfaces." According to O'Reilly, Heberden's nodes are not a part of, and rarely occur in, "osteoarthritis" (only once in 50 consecutive cases): "their pathology has nothing in common with osteoarthritis."

[In our opinion Heberden's nodes merely represent the nodular, bony processes at the terminal phalangeal joints which are but a part of the soft tissue, cartilage and bone reaction of primary hypertrophic arthritis at those joints; in the late stages of this process cartilaginous destruction and lateral displacement of the joint may occur.—Ed.]

Overweight affected only 12 per cent of O'Reilly's patients. In hypertrophic arthritis, pain results from capsular changes, according to O'Reilly; only those motions which stretch the capsule produce pain. Synovial changes and capsular fibrosis account for the stiffness; muscle wasting,

"some of which is constant," produces the weakness. Other features considered characteristic by O'Reilly will be noted later.

Roentgenograms. The usual changes were reviewed.[84, 235, 511, 563, 604] Using an "improved technic," roentgenograms of flexed knees, Jordan [352] and Holmblad obtained better views of intercondyloid fossae, thereby noting early osteo-arthritic changes not visible in ordinary roentgenograms.

Pathology. The pathologic reactions were reviewed.[511]

Laboratory Data. Blood counts in a few cases were normal.[511] Arneth counts were generally normal; occasionally abnormal in either direction.[372] Sedimentation rates were normal in 100 per cent of 25 cases,[28] and in 83 per cent of 53 cases [511]; they were normal in only 59 per cent of Lautman's 82 cases. Saline absorption tests gave negative results.[372] Glucose tolerance tests gave negative results in 13, slightly positive results in three of 16 cases.[372] Among 26 cases, blood creatine was increased in none; creatinine in 31 per cent. Urine contained creatine in 8 per cent; increased creatinine in 8 per cent (Moreno). Hepatic dysfunction, as determined by the rate of excretion of azorubin S, was present in four of 15 cases (Rawls, Weiss and Collins).

Etiology and Pathogenesis. Ray accepted hereditary "articular inferiority" as one of the chief causal factors. The cartilaginous changes due to normal wear and tear were called "attrition lesions"; their exaggeration by chronic trauma (from knock knees, loose bodies, obesity, lax ligaments and muscles) leads to hypertrophic arthritis (Collins). Such changes resulted in knees of rabbits when Bennett and Bauer experimentally produced chronic (four to 28 weeks) patellar displacement; degenerative and hypertrophic changes in cartilage, eburnation of subchondral bone, connective tissue proliferation and marginal overgrowth at the perichondrial margins of articulating surfaces developed. Similar reactions were noted in a case of chronic bilateral patellar displacement.

Little or no support was found for the theory that local or general degenerative vascular changes cause the disease. Among 56 cases, O'Reilly found elevated blood pressures in 36 per cent; myocardial degeneration in 16 per cent; thickening and tortuosity over superficial arteries in 16 per cent; incidences normal for the age group. Furthermore, examination of the small vessels in joint tissues disclosed no signs of disease. According to Kling, interference with articular blood supply from juxta-articular adiposis dolorosa may be one of the causes of hypertrophic arthritis. Painful fatty masses were present in 10 to 15 per cent of his cases of hypertrophic arthritis. Each of 112 patients with juxta-articular adiposis dolorosa complained of pain and disability in contiguous joints and, in a large number, osteo-arthritic changes of varying degrees developed (articular spurring in 57 per cent). The fatty masses presumably interfere with articular circulation by diverting blood from the deep articular tissues (capsule and periosteum) and also by obstructing (through pressure) the blood flow in deep veins, favoring varicosities therein. Kersley found no char-

acteristic changes in nail-bed capillaries. No definite evidences of *endocrine disturbances* were noted.[511]

Factor of infection; bacterial; mycotic. It was generally agreed that bacterial infection seemed to play no rôle but O'Reilly gave a novel slant to the infectious theory. He expressed the belief that osteo-arthritis is a degeneration of joint tissues consequent on chronic inflammatory changes in the lymphatic connections of the joint and due to mycotic infection of the skin of the feet.

O'Reilly's argument follows: The only joints affected in (true) "osteoarthritis" are hips, knees, and lower spine. For reasons which were rather cursorily given, he stated that all the hypertrophic bone changes occasionally seen in other joints are "osteoarthritic changes" secondary to known causes such as gross trauma or fracture; "these osteoarthritic changes are not osteoarthritis," nor are they a part of the disease. Heberden's nodes were excluded as having nothing in common with osteoarthritis. In 50 cases, joints affected were lower spine in 48, left knee in 45, right knee in 41, left hip in 36, right hip in 31 cases; in 21 cases all five regions were affected. "A disease whose incidence in the body is so constant must have an anatomical path of spread. The lymphatic connections of joints provide this path." In 68 per cent of his cases he noted in roentgenograms, small, discrete, calcified lesions in the pelvis, found at necropsy to be calcified tissue in lymph nodes along pelvic vessels. Microscopically, the iliac (but not the popliteal or epitrochlear) nodes gave evidence of chronic inflammation with fibrosis and occasional focal calcification in the fibrotic lesions. O'Reilly sought an explanation of the adenitis. In all cases he found in the feet erosions, whitish patches of sodden skin, not infrequently fissured, in the fourth interdigital space, generally also infections of toe-nails (yellow tinge, loss of translucence, brittleness going on in neglected cases to onychogryphosis). On cultures of affected skin and nails in 20 cases monilia grew in 19; epidermophyton in one. The foot infection was considered responsible for the inguinal adenitis which in turn was the cause of the iliac adenitis (iliac nodes receive lymph from inguinal nodes). Joints and the lymphatic system are closely connected, as synovial membrane is richly supplied with lymphatic vessels. "The iliac glands form a theoretical focal point from which a disease process spreading along the lymphatics would involve the joints which are actively involved in osteo-arthritis" (knees, spine, hips). Joints of the feet and ankles are not involved because they are connected, not with infected inguinal or iliac nodes, but with noninfected popliteal nodes.

[This explanation seems very hypothetical. We do not consider it proved that primary hypertrophic arthritis affects only the joints stated. It is necessary for O'Reilly to make this assumption; otherwise his anatomic explanation would be more difficult to prove. Isn't the skin of the toes connected with the same lymphatic structures as the joints of the toes? If so, in the presence of a foot infection, why aren't the popliteal nodes, which drain the joints of the feet and ankles, infected and why aren't the toe joints not less, but more, likely to be involved? The idea seems unproved.—Ed.]

Treatment. Although little can be done to correct the senescent changes which are the basis of hypertrophic arthritis, by improving working conditions much can be done to lessen the factor of occupational or other chronic trauma which accelerates the senescent lesions (Buckley; Race). Buckley regarded no treatment as of the slightest use for osteophytic outgrowths or Heberden's nodes. Diets, with restrictions of carbohydrates, seemed value-

less (Cmunt) except as they help to remove trauma of obesity (Buckley). Removal of foci was approved only for local reasons, or as a matter of general hygiene (Hamilton; Snyder). Those who have prescribed sulfur or concentrated vitamin D have made little or no distinction between atrophic and hypertrophic arthritis, claiming results in both types indiscriminately. Farley and Steck considered massive doses of vitamin D very helpful. Sulfur was advocated by Clark, Wheeldon, Woldenberg, and Parmenter; of Parmenter's 22 patients so treated, 81 per cent were variously improved, the rest were not relieved. Gold therapy was considered by Hartfall, Garland and Goldie relatively unimportant for hypertrophic arthritis: of 68 patients treated, none were cured; improvement was marked in 10 cases, moderate in 11, slight in 19, absent in 22; six patients became worse.

"There seems little scientific basis for" the continued use of vaccines in hypertrophic arthritis (Jordan).[351] Injections of chaulmoogra oil provided only slight temporary analgesia (Robinson).

Literature on roentgenotherapy for hypertrophic arthritis was briefly reviewed by Fineman and by Kahlmeter. Various opinions on its value have been expressed, in the main favorable (Hernaman-Johnson). Kahlmeter considered its effects purely analgesic. Pains in osteo-arthritic hips seemed to him to arise not so much from intra-articular changes as from painful hyperfunctioning muscles of hip, thigh and back. Roentgen-rays may have some direct influence on these painful muscles. Of 10 cases in which *fever therapy* was given by Simmons, late results were: no relief in five; marked improvement in one; moderate relief in two; slight relief in two. Bierman's results were "poor" (no details). Iontophoresis with *mecholyl* (acetyl-beta-methyl choline) seemed of value to some: of 47 patients of Martin and Eaton, 26 per cent became "well"; 53 per cent were improved; 24 per cent not improved. Six of nine patients of Boyd, Osborne and Markson noted decreased pain and increased motion; three were unimproved. Kling and Sashin preferred *histamine* iontophoresis: of 51 patients, 33 (65 per cent) were "cured or improved"; the rest were not. Among Young's 10 patients treated with histamine ointment, improvement was marked in five; absent or slight in the rest. The oral use of thyroid or iodides was recommended by some (Kersley; Ray). To O'Reilly the early treatment of monilia infections of feet seemed most important.

Physical therapy. The various forms of physical therapy used for atrophic arthritis were advocated for hypertrophic arthritis also. Immersion of hands, covered by rubber gloves, in hot water 20 minutes daily was recommended.[563] The effect of short wave therapy was only that of heat.[355] For painful hips caliper splints properly applied may relieve pain but often are considered more uncomfortable than the pain.[84, 563] New braces for knees [352] and for hips [376] were described. To relieve pain in affected basal thumb joints Ray advised molded leather wrist casings.

Surgical procedures. These occasionally may be indicated for painful hips. Henderson evaluated the various orthopedic measures and considered

manipulation under anesthesia, celiotomy and remodelling of a femoral head, each useful for maintaining or increasing motion in selected cases. Arthrodesis is rarely acceptable to patients. Judgment was reserved regarding acetabuloplasty. A " new " procedure, bone puncture or forage (used by Nobel Smith 1890; by Mackenzie 1931, 1932, 1936; by Graber-Duvernay 1932, 1933, 1935) was employed by Henderson and Simpson in 12 cases of painful hypertrophic arthritis of hips: seven noted " definite lasting relief " from pain; two received temporary relief but pain gradually returned within six months; three noted no relief. Relief of pain was noted during the first postoperative week in five cases (but was lost in one case), three months after operation in one and seven months after operation in another. [This raises the question as to the relation of the relief to the operation.—Ed.] Bone drilling of femoral epiphyses seemed of value only in cases in which the arthritis was advanced. The procedure was relatively simple. Patients stayed in the hospital an average of only 10 days and were usually out of bed, walking, seven or eight days after operation.

Backache and Sciatica

General Remarks. In the past it has often been so difficult to find the exact cause of any given back pain, and patients have been so unsatisfactory to treat that they have been accepted with distaste and pessimism by most physicians; a backache was just another " headache " to the physician. The problem is still a complex one and as Galland wrote, " a discussion of low back pain should be entered upon with a spirit of humility, for this is a topic upon which no physician in the present state of knowledge has the right to be dogmatic." Because of recent advances in knowledge of the pathologic physiology of the back the interest of physicians therein has greatly increased and papers on the subject have increased accordingly. It is impossible to review them adequately here, filled as they are with a mass of clinical and statistical details concerning the inter-related anatomic, roentgenologic, neurologic and pathologic aspects involved.

Causes of Backache and Sciatica. Major causes of backache were listed [616] as (1) neurologic, (2) gynecologic, (3) genito-urinary, (4) orthostatic (postural and from developmental anomalies) and (5) osteo-arthritic. Detailed working classifications [253, 254, 458] were given (table 2). Causes of backache and sciatica, particularly low back pain, are so numerous that a proper study involves careful local and general physical examinations, frequently special examinations (neurologic, urologic, gynecologic), roentgenograms often made at various angles (anteroposterior, lateral, oblique, stereoscopic), often examination of spinal fluid and spinal roentgenograms with injections of lipiodol. The technic and significance of the various tests and physical maneuvers for localizing and differentiating lesions affecting the lower back were again discussed.[23, 254, 256, 451, 470, 501] Roentgenologic methods for studying spines and the special points to be noted were discussed.[23, 254, 320, 485] Special technic and especially careful interpretation are

required to demonstrate smaller lesions such as those of facets and of intervertebral foramina.

TABLE II

CAUSES OF LOW BACK PAIN

(*Ghormley* [253, 254])

1. Posture:
   (*a*) Chronic postural strain:
      1. Lumbosacral or sacro-iliac lesions
2. Trauma:
   (*a*) Trauma involving vertebrae:
      1. Fracture
         (*a*) Bodies
         (*b*) Pedicles—may produce spondylolisthesis
         (*c*) Laminae
         (*d*) Facets
   (*b*) Trauma involving joints:
      1. Traumatic spondylosis
   (*c*) Trauma involving disks:
      1. Narrowing of disk
      2. Avulsion of disk
      3. Rupture of nucleus pulposus
3. Infection:
   (*a*) Arthritis, infectious
   (*b*) Spondylitis deformans or *spondylose rhizomélique*
   (*c*) Fibrositis
   (*d*) Typhoid spine
   (*e*) Tuberculosis, etc. (real localized infections)
4. Metabolic and senescent conditions:
   (*a*) Hypertrophic changes (may be traumatic)
   (*b*) Osteoporosis with pathologic fracture
5. Congenital anomaly:
   (*a*) Spina bifida
   (*b*) Sacralization of fifth lumbar vertebra or lumbarization of first sacral vertebra
   (*c*) Anomalous facets (may produce spondylolisthesis)
6. Neoplastic conditions:
   (*a*) Benign tumors:
      1. Osteoma and osteochondroma
      2. Giant cell tumor
      3. Hemangioma
   (*b*) Malignant tumors:
      1. Metastatic from prostatic and mammary carcinoma, etc.
      2. Myeloma
      3. Primary osteogenic sarcoma
      4. Ewing's tumor, etc.
7. Neurologic conditions:
   (*a*) Tumors of spinal cord, etc.

(*McDeed* [458])

1. Inherent normal variations.
   A. Transitional types of vertebrae
   B. Jointed { transverse processes / articular processes
   C. Asymmetrical joints
   D. Incomplete closure of neural arches
   E. Wedge-shaped vertebrae
   F. Synostosis of vertebrae
   G. Styloid processes at bases of transverse processes
   H. Variations in shape and position of transverse processes
2. Acquired.
   A. Scoliosis
   B. Traumatic arthritis
   C. Herniation of nucleus pulposus into body of vertebra (due to faulty posture)
3. Traumatic.
   A. Fractures, or
   B. Dislocations of bodies or accessory parts
4. Disease.
   A. Causing destruction
      1. Tuberculosis
      2. Malignant new growth
         (*a*) Carcinoma
         (*b*) Sarcoma
         (*c*) Myeloma
      3. Destructive benign tumors
      4. Osteomyelitis
   B. Producing new growth
      1. Osteomyelitis (destructive or constructive)
      2. Arthritis
      3. Syphilis
      4. Benign tumor
         (*a*) Osteochondroma
         (*b*) Osteoma
         (*c*) Myositis ossificans traumatica
         (*d*) Osteitis deformans (Paget's disease)
         (*e*) Exostosis
      5. Disease of uncertain etiology
         (*a*) Rachitis
         (*b*) Chondrodysplasia
         (*c*) Osteogenesis imperfecta
         (*d*) Osteomalacia
         (*e*) Osteitis fibrosa cystica, etc.

Backache from Urologic Lesions. Diseases of the kidney and upper urinary tract usually produce acute or chronic "high backache," generally unilateral, occasionally central or bilateral, often with pain referred to scrotum. Lesions of the prostate and urethra generally produce perineal

pain, less commonly low back pain.[14, 253, 589] Diagnosis rests on the appearance of localizing symptoms and on results of urologic examination.

Backache from Gynecologic Lesions. The pelvis should be carefully examined in all cases of backache and sciatica [253, 616]; however, gynecologic lesions are not common causes and uterine displacements per se have little or no relation to backache, according to Mercer. Backache due to gynecologic lesions is more likely to be exaggerated during menses than that due to skeletal disease. Back pain from intrapelvic tumors is likely to be chronic and intractable with little or no intermittency.[612]

Backache and Sciatica from Postural Abnormalities. Characteristics of this syndrome were reviewed by Mercer and Wesson. Correction of posture by postural and gymnastic exercises relieves the condition.

Backache Due to "Functional Decompensation." This is the commonest type of low back pain, according to Hauser. An imbalance exists between the functional capacity of a back and the demands made on it, producing chronic fatigue; sore, stiff, back muscles; aching pain low in the back; sometimes sciatica; an increase of all normal spinal curves. Roentgenograms are negative until secondary changes occur. Treatment was outlined: rest, physical therapy and the use of certain exercises (described) to restore normal posture, muscle strength and reserve capacity.[302]

Backache from Senile Osteoporosis. The condition, described by Ghormley, affects many more females than males, usually but not always more than 50 years of age. Pain may be severe and is usually of the "static type," relieved by rest, worse after activity. Roentgenograms show general spinal osteoporosis, sometimes pathologic fractures and ballooning of intervertebral disks as the expansile strength of disks takes advantage of the weakened vertebral bodies. The cause is unknown: Blood calcium and phosphorus are normal in this condition; they may be low in osteomalacia, and pelvic and other bones are affected in addition to the spine. Treatment included the use of a Taylor brace, a diet high in calcium and vitamins, tribasic calcium phosphate 4 gm. t.i.d.; and adult doses of vitamin D (cod liver oil, haliver oil, viosterol). Treatment must be prolonged; improvement rarely occurs in less than three to four months [or longer.—Ed.]

Backache and Sciatica from Tight Fascia Lata and Iliotibial Band. Ober again discussed this condition. Patients so afflicted are uncomfortable lying on their backs or abdomens, and generally they lie on their sides with knees flexed. According to Ober, signs of abduction contracture are generally but not always present (positive Ober test), straight leg raising is limited, and roentgenograms are negative. Kimberley did not consider Ober's test diagnostic of this condition. Before recommending fasciotomy Myers differentiates between organic and spasmodic contracture of iliotibial bands by the use of a general anesthetic; this will not relieve organic contractions. Results of fasciotomy were noted: Of 415 patients so treated relief was complete in 75 per cent, partial in 4 per cent, absent in 21 per cent (Ober). Smith treated 49 patients who had sciatica and tight fascia lata

and iliotibial bands. Of 20 treated by fasciotomy alone results were excellent or good in 75 per cent of cases, failure in 25 per cent; in 20 treated first by lumbosacral fusion, later by fasciotomy for persistent sciatica, results were excellent in only 20 per cent of cases, good in 5 per cent, poor in 75 per cent; of nine patients treated by fusion and fasciotomy six were completely relieved, three unrelieved. Fasciotomy in selected cases was approved without detailed comment by Ghormley, Myers and Smith.[628] Others found it difficult to select which patients will respond favorably and considered the rationale of fasciotomy unexplained.[375, 451] Kimberley considered it often very useful but less so than fusion.

Relation of Pyriformis Muscle to Sacro-Iliac Backache and Sciatica. The pyriformis muscle originates in part from the capsule of the sacro-iliac joint and is closely related anatomically to the sciatic nerve; the latter is found to pierce the muscle of 10 per cent of cadavers. When a sacro-iliac joint is diseased the pyriformis muscle may be in spasm or actually diseased; in certain cases this may produce hyperemia of the sheath of the trunk of the sciatic nerve and may produce sciatica; such is Freiberg's concept. Myotomy of the pyriformis muscle may give relief in such cases. Freiberg believes that results from Ober's fasciotomy may be accomplished by release of pressure on a pyriformis muscle and sciatic nerve.

Backache from Developmental Anomalies. Studies on the incidence and significance of developmental anomalies in the lower back were reported.[130, 375, 379, 725] As causes of low back pain and sciatica they are much less important than lesions secondary to diseases of intervertebral disks.[379,721] Of Williams' 400 cases, low back pain in 71 per cent presumably was due to disease of intervertebral disks; in only 29 per cent to vertebral anomalies. Such anomalies may be present without clinical significance.[254] However, Hodges and Peck considered them significant causes of sciatica: they were present in 27 per cent of 447 cases of low back pain and sciatica, but only in 14 per cent of 538 cases of low back pain *without* sciatica.

"Facet Syndrome" (Acute Traumatic Subluxation). Nine cases of this syndrome described by Ghormley (1933) were discussed by Troedsson. Characteristic was the sudden onset of low back or sciatic pain after some activity, often trifling, involving a twisting or rotary strain of the lumbosacral region. Muscle spasm and sciatic scoliosis may ensue. It is difficult for patients to bend forward, sit down, stand up or remove shoes. Pain is of variable severity and may persist until muscle spasm subsides or until surfaces of facets change their position by active or manipulative movement. Roentgenograms in ordinary positions are generally negative; disease of facets is best, or only, shown in oblique views. Pathologic reactions found in facets were generally those of traumatic (not infectious) arthritis: fibrillation and degeneration of cartilage and eburnation of underlying bone.[254] Troedsson assumed the presence of a minute subluxation of one or both inferior articular processes of the fifth lumbar vertebrae in his nine cases: simple manipulation without anesthesia was uniformly successful.

Syndromes Resulting from Disease of Intervertebral Disks. According to current writers most cases of pain in neck or low back, or sciatica are not due to "arthritis" of the spine but are secondary to alterations in intervertebral disks and are rather late manifestations of "discogenetic disease." The commonest site of these lesions is in the lower cervical and lower lumbar region. Their pathogenesis was clearly outlined by Oppenheimer and Turner and by Williams in an excellent series of papers illustrated by diagrams and roentgenograms. Features of discogenetic disease of the cervical region are less well known than those of the lumbar region. Of 72 patients referred to Oppenheimer [508] for "arthritis or rheumatism" of neck and shoulders only one had arthritis, 66 had narrowed cervical intervertebral foramina from discogenetic disease, three had cervical ribs; in two cases roentgenograms were negative. Symptoms in the cases of Oppenheimer and Turner were those of segmental neuritis: pain in shoulder girdle, between shoulder blades, over precordium, *rarely in the neck;* weakness and sometimes atrophy of shoulder muscles. The following train of events was noted: Constantly present was "primary" thinning of intervertebral disks (i.e., thinning not due to nuclear prolapse) which produced a narrowed intervertebral space. The cause of the thinning was generally assumed to be acute or chronic trauma from injury or faulty posture; many patients habitually stretched their necks forward. The narrowing of the intervertebral spaces produced subluxation of articular facets, but actual primary arthritis of facets was practically never noted (only once in 50 cases). The displacement of articular facets constricts the cervical foramina, demonstrable in oblique roentgenographic views; pressure on nerve roots results. Sometimes additional effects of the narrowing of intervertebral disks were noted; vertical (not posterior) nuclear prolapse; formation of exostoses on the anterior and lateral borders of the vertebral bodies. The exostoses are often said to be evidence of "hypertrophic arthritis" but are really not arthritis, as the intervertebral space is not a joint but a synchondrosis. The pressure on nerve roots cannot be caused by exostoses in these positions, and segmental neuritis was noted, even without such exostoses. In these cases Oppenheimer and Turner noted no loss of cervical flexibility as a whole, for this is not disturbed as long as four or more disks remain normal. In each case there was exact correlation between the segmental neuritis and the cervical disks affected.

Symptoms Due to Narrowed Intervertebral Foramina. Syndromes resulting from constriction of intervertebral foramina at various spinal levels were discussed in detail by Mooney and Willis but especially by Oppenheimer. The size of the foramina may be reduced by (1) collapse or (2) constriction of foramina. Collapse of intervertebral foramina may result from softening of intervertebral disks (from trauma), from rarefaction of articular processes (a rare condition of unknown etiology, occasionally affecting the pedicle of the sixth cervical vertebra), or from disease of vertebral bodies ("discogenetic disease"). Collapse of foramina begins

at anterior margins of foramina and may produce "hypertrophic arthritis" (vertebral exostosis). Constriction of foramina generally results from inflammatory swelling of synovial membranes of apophyseal joints of the spine followed by calcification of ligaments and ankylosis of facets (i.e., "spondylarthritis ankylopoietica"; rheumatoid arthritis of apophyseal joints). In these cases constriction begins at the posterior margins; disks are not involved and segmental neuritis is less common since the size of foramina is less reduced than in cases of discogenetic disease with collapse of foramina.

Treatment of "Discogenetic Disease" and Narrowing of Intervertebral Foramina without Nuclear Prolapse. Oppenheimer recommended head traction and neck stretching (Hanflig 1936) for cervical lesions, lumbosacral fusion for low back lesions. Williams reduced lumbosacral lordosis and restored the size of foramina by the use of a plaster of paris jacket; later, postural exercises and a "lordosis brace" worn six to 12 months. If these measures failed he advised lumbosacral fusion and facetectomy but only in cases of low back pain with segmental symptoms.

Backache and Sciatica from Posterior Prolapse of Disk or Nucleus Pulposus. This syndrome was further clarified in the excellent reports of Barr, Hampton, Mixter and Robinson and of Love and Camp. Vertical prolapse of disks is more likely to occur after severe trauma; horizontal (posterior) prolapse is more likely to result from less severe, even mild trauma received when the spine is in flexion.[428, 616] The factor of trauma was present in 60 to 80 per cent of the cases of posterior prolapse seen by Barr, Hampton and Mixter. Often shortly thereafter, pain appears. The prolapse may produce low backache or lumbago like that from many other causes, or root pain (especially sciatic) may be present, usually unilateral and often intractable. Pain is accentuated by coughing or sneezing or by whatever increases intraspinal pressure. Partial or complete remissions of pain are common. Numbness, tingling or weakness of a leg may be present; in severe and late cases, paralysis of an extremity or of sphincters may occur.[34] But often (in 50 per cent) neurologic symptoms and signs are absent except perhaps for diminished Achilles tendon reflex and a positive Laségue sign on the affected side. Decreased lordosis is usually present, sometimes sciatic scoliosis or kyphosis. None of these physical, neurologic or orthopedic signs is specific for this syndrome. Of the patients of Love and Camp, four had pain in neck or upper extremities, 26 had low back pain with sciatica, 11 had sciatica only, four had low back pain without sciatica; symptoms averaged 1.4 years before diagnosis was confirmed by operation.

Preoperative diagnosis depends on visualizing a filling defect in roentgenograms after injection of lipiodol, but since lipiodol may occasionally have irritating properties, cases for such injections are selected by preliminary tests. If a patient with low back pain and sciatica presents the neurologic symptoms and signs noted, the spinal fluid is examined and a

Queckenstedt test (for subarachnoid block) is made; the latter is generally negative but is of great significance if positive. Love and Camp considered of great significance the presence of a positive "reverse Queckenstedt test"—the duplication or exaggeration of low back pain or sciatica during the injection of 1 per cent procaine solution into the caudal epidural space. The spinal fluid protein is generally (in 75 per cent) increased (more than 40 mg. per 100 c.c.). It was increased in 52 of 58 cases of Barr, Hampton and Mixter; in 30 of 41 cases of Love and Camp; in the latter's cases it varied between 20 and 360 mg. per 100 c.c. A normal concentration of protein in spinal fluid does not rule out prolapse of a disk. One should obtain fluid as low in the spine as possible and examine the first 2 to 5 c.c. collected; otherwise the protein may be normal. If the reverse Queckenstedt test or the spinal fluid protein test, or both, are positive one is justified in injecting lipiodol for the demonstration of filling defects. Before this is done, however, some make an "aerogram," a caudal roentgenogram after injection of air; if this is normal, some consider injections of lipiodol not indicated.[616] Ordinary roentgenograms are generally normal or at least of little significance; narrowing of disks may be apparent but often does not coincide with the symptom-producing lesion, hypertrophic changes are likewise of no localizing value. The technic and interpretation of roentgenographic studies with lipiodol were clearly described by Hampton and Robinson, by Barr, Hampton and Mixter, and by Love and Camp. No less than 5 c.c. of oil should be injected; smaller amounts proved unsatisfactory. Such studies were "90 per cent accurate" in the hands of those mentioned. No false positives were noted. [Occasional "false positives" have since been encountered.—Ed.] Therefore laminectomy should not be performed if such studies are negative. The great value of such studies far outweighs the slight risk of producing irritation; in more than 100 cases no permanent ill effects were noted (Hampton and Robinson).

Treatment. Prolapsed disks may be discovered at levels unrelated to symptoms; unless symptoms of pressure on the cord or spinal roots are present and unless the level of symptoms corresponds to the level of the lesion in roentgenograms, surgical treatment is not indicated. Relief, usually prompt and complete, results from laminectomy and removal of the protruded material. In the 50 cases of Love and Camp, lesions were lumbar in 38 (multiple protrusions in six), thoracic in seven, cervical in five cases. Results were complete relief in 33, partial in 15, none in two; there were no postoperative deaths. Among 58 cases Barr, Hampton and Mixter noted these results: complete relief in 32, partial relief in 12, no relief in two, results too recent to evaluate in eight; one postoperative death, three later incidental deaths. Love and Camp did not advise the use of bone grafts or the postoperative use of braces or casts; Barr, Hampton and Mixter occasionally advised bone graft after laminectomy if patients were

doing heavy work. Excellent results from laminectomy were noted in six cases of others.[98, 616, 620, 625]

Low Back Pain and Sciatica from Hypertrophy of Ligamenta Flava. These ligaments connect the laminae of contiguous vertebrae, blend with interspinous ligaments and help to form the capsules of joints between articular facets; the lateral edges of these ligaments form the posterior margin of intervertebral foramina. At times they increase in thickness so that they encroach on the spinal canal and compress the cord at any level but especially at the fourth and fifth lumbar vertebrae. Spurling, Mayfield and Rogers, and Brown [81] reported 14 such cases. Symptoms were similar to those from protruded disks: chronic low back pain, after trauma, generally with sciatica, sometimes numbness of leg or buttock, muscle atrophy or weakness, postural deformity, diminished or absent Achilles tendon reflexes; complete spontaneous remissions may last a few weeks to several years. Roentgenograms by ordinary technic reveal nothing significant; those after injections of lipiodol reveal filling defects. Treatment consisted of removal of involved laminae and ligaments; results should be as satisfactory as those from removal of protruded disks.[81] Of seven patients so treated, prompt relief was noted in six; there was one postoperative death.[647]

Treatment of Low Back Pain and Sciatica: General Comments. Obviously low back pain and sciatica arise from infinite causes; sciatica is merely a name for a regional pain caused chiefly by injury or infection. Among other infections, undulant fever may cause sciatica.[19, 222] Reduced skin temperatures in affected legs suggested to Eldbloom and Ingvar that ischemia may be a factor in sciatica; vasodilators were used in treatment. All patients with sciatica deserve neurologic examination.[254] In certain cases of sciatica, roentgenotherapy seemed valuable [325, 354]; short wave therapy seemed useful to some,[570] useless to others.[355] Sulfanilamide is not indicated.[714] Symptoms and treatment of sciatic scoliosis were noted by Kleinberg, Watson-Jones, and Levine; the latter reviewed 80 cases. Rest in bed, physical therapy, and belts were used in mild cases; traction, caudal block, plaster jackets, injections into the sciatic nerve in severe cases; fusion operations in intractable cases. Manipulation of the spine under anesthesia was used by some, disapproved by others.[254, 325] Wardle relieved 26 patients by fixation in "head suspension plasters."

When the cause of low back pain or sciatica in a given case is not clear, rather than advising surgical procedures physicians should use conservative methods and allow time to clarify the diagnosis.[612] Measures recommended in acute cases were rest in bed, a firm mattress, use of Bradford frame or "fracture bed" [250, 254, 287, 375, 470, 518]; head or pelvic traction if much muscle spasm was present [250, 470]; use of a small pillow under the lumbar region [470] or a scultetus bandage [254]; adhesive supports are only occasionally applicable as physical therapy is more important. In ambulatory cases supports of one sort or another, physical therapy and graded exercises, especially swimming, were advised.[254, 470] In resistant cases some

used rest in bed, traction, lumbar supports and physical therapy [254]; others used epidural injections [250, 489]; Kimberley believed the latter useless. Manipulations in selected cases were approved by some [250, 327, 451, 470, 489] who described various methods; manipulation was disapproved by others.[375]

Indications for Fusion Operations. Those of Ghormley and Wesson were (1) persistent low back pain with or without sciatica, (2) failure of conservative therapy, (3) presence of narrowed lumbosacral disk or facet changes or both, (4) negative neurologic examination, (5) consistently localized tenderness, (6) static type of pain (if rest won't give even temporary relief, fixation will not help); (7) patients aged 20 to 50 years. In such cases results from various types of fusion were satisfactory in a high percentage. Compere listed contraindications for fusion: (1) low back pain with infectious arthritis, (2) unsettled compensation cases, (3) elderly or "poor-risk" patients, (4) girls before puberty. Compere preceded fusion operations with vigorous stretching and manipulation. A conservative attitude toward fusion is required. Among 139,000 patients at the University of Chicago clinics were 2242 with low back pain; only 76 patients (3.4 per cent) were subjected to fusion (Compere).

"Platyspondylia Aortosclerotica." This term was applied by Oppenheimer to a syndrome "not found described." Six patients presented marked calcification of the thoracic and abdominal portions of the aorta with a systemic spinal disease characterized roentgenographically by demineralization of vertebral bodies, collapse of midthoracic and upper lumbar bodies, pronounced expansion of intervertebral disks into softened vertebrae. Other parts of the skeleton were unaffected, apophyseal joints of the spine and intervertebral foramina were free. In the longitudinal ligaments sometimes there were small calcifications. There were no signs of metabolic or endocrine disorders, or of peripheral or cerebral arteriosclerosis. Except for the gradual formation of a gibbosity the disease did not cause marked subjective symptoms.

[To us these cases represent, not a new disease but senile osteoporosis with coincidental aortic sclerosis.—Ed.]

Spinal Malignant Growths and Other Lesions. Malignant neoplasms must always be considered if progressive low back pain is unrelieved even temporarily or partially by ordinary measures. Early cases of malignant disease coincidentally associated with developmental anomalies or "hypertrophic arthritis" of the spine are especially likely to be missed.[137,254,458] Features of some unusual spinal lesions were described: hemangioma [255]; vertebral osteomyelitis with infection of epidural spaces.[77]

Post-Traumatic Neurosis of Spine. A post-traumatic neurosis often represents "a protest of labor against capital." [234] In such cases symptoms may resemble those due to organic change (muscle spasm, abnormal posture and gait, hypertrophic changes) but neurologic signs and muscle atrophy are generally absent, or unphysiologic areas of anesthesia are present, and

patients respond to placebos and psychotherapy; electricity, simple injections and supports are used as media for the latter. Some patients cling to their braces even at night: "Their brace supports their claims more than their vertebral column. . . . Physicians must look beyond the back to the background" which is often that of a person dissatisfied with work or with life, at conflict with reality (Fetterman). [A diagnosis of post-traumatic neurosis should be made only with the greatest care. Most cases of backache are caused by real organic or functional disability.—Ed.]

"Spine Malingerers." Consistently localized tenderness is of great help in distinguishing organic disease from malingering. Most experienced examiners can tell whether a patient's response to percussion or palpation is overdone or feigned. Malingerers never time their responses accurately; they are usually too quick, sometimes too slow. Their attitude in other ways is often characteristic of the "compensation neurotic" and gives them away (Ghormley).

Spondylitis

Two types were again described: (1) atrophic spondylitis (spondylitis ankylopoietica) and hypertrophic spondylitis (spondylitis osteo-arthritica) corresponding respectively to atrophic and hypertrophic arthritis in other regions. Scott noted three types: (1) "spondylitis adolescens" (spondylitis ankylopoietica), (2) spondylitis osteo-arthritica, and (3) spondylitis as a late manifestation of "infective polyarthritis." In the first type "sacroiliac joints are always abnormal"; in the latter two types "sacroiliac joints are always normal," according to Scott.

Atrophic Spondylitis (Spondylitis Ankylopoietica). The usual clinical and roentgenographic features were described.[263, 406, 605, 689] A case with prominent neurologic symptoms was described (Ziskind and Ziskind). The disease was regarded as the spinal equivalent of atrophic (rheumatoid) arthritis by some[39, 689]; as a different disease by others.[169, 263, 605] If it is the same as atrophic arthritis (which affects females more than males) why does atrophic spondylitis affect males from four to 14 times as often as females? Scott again elaborated his thesis (reported in previous Reviews) that the first demonstrable lesion is always in sacro-iliac joints, presumably infectious, bilateral sacro-ileitis which long antedates the spinal symptoms of "spondylitis adolescens." No organisms had been recovered from sacro-iliac joints, however. According to Buckley,[85] Scott's thesis has not yet been proved: "One meets with cases occasionally with typical ankylosing changes in the upper spine in which the sacroiliac joints are not affected till later." Oppenheimer,[507, 508] who regarded this disease ("ankylosing spondylarthritis") to be atrophic arthritis of apophyseal joints, stated that by newer roentgenologic methods (described) for visualizing facets and foramina one can generally note involvement of lower thoracic apophyseal and costotransversal joints, sometimes several years before sacro-iliac involvement.

Treatment. Scott advised early search for the sacro-iliitis among young persons with wandering back and thoracic pains, and repeated wide-field roentgenotherapy. Results were not given but were presumably satisfactory. However, Gordon considered "deep x-ray therapy," foreign proteins and vaccines "absolutely contraindicated." The usual measures were recommended: rest in bed, plaster support, hyperextension frames, postural and deep breathing exercises, nutritious diet, removal of foci of infection.[263, 406, 507, 689] Hartfall, Garland and Goldie gave chrysotherapy in 18 cases: there was "marked improvement" in five, no patients were cured. Gold, fever therapy and vaccines were "disappointing."[689]

Hypertrophic Spondylitis (*Spondylitis Osteo-Arthritica*). The current concept is that this is not true arthritis but spondylosis, only an exostotic reaction to mechanical irritation arising from alterations in vertebral bodies and in intervertebral disks. In hypertrophic spondylitis disks and vertebral bodies are frequently narrowed; in atrophic spondylitis disks are not narrowed.[263, 507] Osteo-arthritis is not a common cause of low back pain with sciatica, according to Hodges and Peck: it was present in 24 per cent of 447 cases of backache with sciatica, but also in 28 per cent of 538 controls without sciatica. Of 529 cases of hypertrophic arthritis of various joints, studied by Kuhns, the spine was the cause of symptoms in 294 cases (195 females; 99 males). Average age of the 294 patients was 53 years: 11 patients were 30 to 40 years old; one woman of 28 years, a professional dancer, had marked lumbar hypertrophic changes. In three cases there was coincidental metastatic carcinoma, a possible source of serious errors in diagnosis. Metabolic rates were subnormal in only 17 per cent. Symptoms were exaggerated by trauma, also by intercurrent infection, e.g., colds. Gillespie noted a case with marked cervical hyperextension and neurologic manifestations simulating amyotrophic lateral sclerosis. Fibrositis is a common accompaniment of hypertrophic spondylitis (Gordon).

Treatment. The usual methods were advised: rest if necessary in a plaster shell, supports, physical therapy. Roentgenotherapy seemed useful to Kahlmeter. Head traction was approved by Oppenheimer; slight, but not forceful or manipulative, traction was approved by Kuhns. Of the latter's 294 patients, 70 per cent were able to work, 18 per cent were not, 12 per cent had died.

[Follow-up period unstated.—Ed.]

Gout and Gouty Arthritis

Clinical Features. Acute gout is less common and less severe than formerly, according to some[346, 553]; it is common but frequently misdiagnosed according to others.[310, 590] The features of typical gout and gouty arthritis were reviewed by Buckley, Copeman, Graham, Hench, Jennings, Rutledge and Bedard, and Volini. The classical pattern of gouty arthritis was generally accepted as being one of recurrent attacks of acute gouty arthritis with complete symptomatic remissions, later, in some cases, chronic

gouty arthritis. The tendency for acute attacks to be seasonal in appearance and consistently related to certain provocatives was well illustrated in a case reported by Rutledge and Bedard: 13 acute attacks were experienced in nine years; of these attacks seven were provoked by the feasting of Christmas-New Year week, three by seasonal occupational trauma, one by other trauma, one by an operation (another attack made worse by an operation), one by no known factor. Of 19 diagnostic features of gout this patient illustrated 13. The clinical features considered by Hench as points useful in the diagnosis of presumptive (pretophaceous) gout were reviewed by Rutledge and Bedard. The tendency for gouty arthritis to involve the more peripheral joints and rarely to affect spine, shoulders and hips was noted.[310] Typical gout is reputedly rare among Chinese: A case of tophaceous gout was reported.[479] A patient of Owen and Roberts with acholuric (hemolytic) jaundice developed recurrent acute gouty arthritis presumably related to excess nucleoproteins from destroyed erythrocytes; splenectomy was performed and both conditions disappeared.

[On the seventh postoperative day acute gouty arthritis occurred. One of us, P. S. H., noted (1935) the frequency and diagnostic importance of acute postoperative gouty arthritis.—Ed.] Garrod's theory that gout results from renal insufficiency has generally been abandoned; renal insufficiency may result from gout but few believe that gout is a symptom of nephritis. Copeman noted a man with tuberculous calcification of both kidneys; progressive renal insufficiency, uremia and hyperuricemia occurred; subsequently two attacks of gouty arthritis, a disease previously absent.

[The relationship may have been coincidental, not etiologic.—Ed.]

Cases of unquestioned (tophaceous) gouty arthritis in which the arthritis comes on insidiously and progresses chronically without complete remissions occur rarely if at all; however, Buckley and Copeman accepted as gout certain cases of arthritis, chronic from the onset, associated sometimes with hyperuricemia (but no tophi) and somewhat relieved by a regimen for gout. [In such cases the hyperuricemia, in our experience, is often due to coincident mild arteriosclerotic nephritis, is not due to gout and is not related to the arthritis.—Ed.]

Several writers continued the argument on the existence of "irregular gout." Pringle spoke of plethoric gout and gouty glycosuria, eczema, phlebitis or bronchitis. The gouty nature of most of these complaints was denied by Buckley, Copeman and Graham and by the majority of Americans interested in gout.[310] However, the authenticity of gouty eczema was entertained by Copeman, that of gouty phlebitis by Buckley. [One of us, P. S. H., recently saw acute phlebitis in a gouty patient; biopsy of the vein revealed no urates therein and measures successful in gouty arthritis did not affect the phlebitis. —Ed.] Acute or chronic "gouty fibrositis" (fasciitis, lumbago, sciatica) was considered by some an accepted feature of the disease amenable to the usual measures for gout.[87, 148, 346]

Laboratory Data. Sedimentation rates in Jennings' eight cases of acute gouty arthritis ranged from 60 to 100 mm. (1 hour; Westergren method). Arneth counts and glucose tolerance tests were normal in Kersley's cases

(no details). Hyperuricemia is generally but not always present, and may be absent even during an acute attack [87, 272, 346, 590, 690b]; its relationship to gout is now usually regarded as of secondary, not of etiologic, importance.[148, 310]

Etiology and Pathogenesis. The usual ideas were expressed by several.[87, 148, 690b] The opinions of various American specialists were reviewed by Hench.

1. Metabolic factors: The uric acid problem. Gout is commonly defined as a disturbance of purine metabolism. Thus Pringle considered it "an error of metabolism in which the liver is the chief offender." However, some, among them Thannhauser (1932), insist that it is not a true metabolic disease; that in gout there is no disturbance of intermediary purine metabolism but an obvious disturbance in the disposition of uric acid; apparently the kidneys of gouty patients simply cannot concentrate and eliminate urates adequately even though they handle other metabolites satisfactorily. Thus, to them gout is not a metabolic disease but some peculiar type of selective renal insufficiency. Studies by Grabfield suggest that some functional disturbance of the vegetative nervous system, involving especially renal innervation, may cause gout.

It has been believed that cinchophen controls the excretion of uric acid by some direct action on renal epithelium but Grabfield and Pratt (1931) concluded from certain experimental data on humans that excretion of urates was accomplished by the action of cinchophen on the central nervous system. This conclusion has now been supported by animal experiments. Cinchophen and other drugs were given to dogs before and after denervation of kidneys. In most dogs a large part of the purines is reduced to allantoin, a small part to uric acid. Dalmatian hounds excrete much more uric acid than allantoin. In both types of dogs, before renal denervation, cinchophen increased the excretion of total nitrogen, allantoin and uric acid. After renal denervation the drug produced increased excretion of the first two but decreased excretion of urates. This reversal of the "uricosuric action" of cinchophen slowly disappeared as renal nerves regenerated. "Had the action of the drug been a simple one on the renal epithelium through its nerve, one would expect denervation to eliminate the action. However, the reversal of effect on the completely denervated kidney cannot be explained on any simple basis and must involve interaction either with some other organ or between the sympathetic or parasympathetic systems." Ergotamine in certain doses blocks sympathetic impulses. When ergotamine was given simultaneously with cinchophen to normal dogs the physiologic effect of cinchophen was cancelled by the ergotamine: the effect on excretion of uric acid was similar to that in the denervated kidney but there was also an elimination of the effect on the excretion of total nitrogen and allantoin (Grabfield, Prescott and Swan). Atropine in adequate doses will block parasympathetic impulses. The use of atropine with cinchophen did not modify the ordinary effect of cinchophen (alone) on urate excretion but eliminated the effect of cinchophen on allantoin excretion. Apparently the effect of cinchophen on allantoin excretion is mediated through the parasympathetics, that on uric acid excretion is mediated by the true sympathetics, and uric acid excretion may be modified by the autonomic nervous system.

Certain clinical observations were correlated with the foregoing. Harpuder (1924) noted that ergotamine reduced the excretion of urates by

normal persons, and Hench (1935) noted the provocative effect of gynergen (ergotamine tartrate) on gouty patients. [The provocative effect was inconsistent and unreliable as a (provocative) test for diagnosis.—Ed.] Grabfield noted a similar case and stated that Thannhauser had also seen precipitation of gout by ergotamine. In Grabfield's case the injection of ergotamine produced urinary diuresis, an absolute *increase* in uric acid excretion but a *reduction* in the urinary uric acid concentration; about seven hours after injection of the drug the patient's great toe became red and painful. These facts suggested that "the gouty attack and uric acid excretion do not necessarily run hand in hand; nevertheless they are both connected with the autonomic mechanism which controls the concentration of uric acid in urine."

2. Factor of allergy. The theory of Llewellyn (1927), Gudzent (1928) and others that acute gouty arthritis represents an allergic reaction to unknown food or bacterial allergens was favored by Buckley, Cmunt and Pringle but was not supported by new data. In America this theory finds little support.

3. Factor of infection. Infection is not the cause of gout but may provoke gouty arthritis.[148, 272, 553] Gout is not due to the local action of an infective agent but sodium biurate may be deposited in joints damaged by bacterial action.

Treatment. Accepted principles and methods of treatment were reviewed.[87, 148, 272, 310, 346, 690b] For acute attacks the following were recommended: an early purge; colchicine; purine free diet; antiphlogistic compresses; cinchophen or salicylates, or salicylates with amino-acetic acid; various types of physical therapy. Gouty patients always should have colchicine handy.[272] It was stressed that the indefinitely prolonged treatment of gouty patients after an attack may modify the disease greatly, and is more important than the treatment of acute attacks. Such "prophylactic" or "interval-treatments" included removal of foci of infection,[148] dietary restrictions of greater or lesser severity, the use of cinchophen or a substitute therefore. Spa therapy may help to prevent attacks but may actually precipitate attacks if injudiciously given at certain phases of gout.[87, 148, 553] Physicians differed in their attitude concerning alcoholic beverages. Some advised the avoidance of all of them; others considered certain forms rather harmless but there was no unanimity regarding the exceptions allowable. The treatment of coincidental infection of the urinary tract of gouty patients with ketogenic diets may provoke acute gout; mandelic acid therapy is preferable.[143]

[Sulfanilamide probably will supplant some of these remedies.—Ed.]

Cinchophen and substitutes. The comparative value of cinchophen and salicylates in gout was discussed in detail in the first Review.[1] Although salicylates augment excretion of urates they were considered less valuable than, and not a satisfactory pharmacologic substitute for, cinchophen. According to some only large irritating amounts of salicylates were effective in

gout. According to others, salicylates may actually provoke acute attacks.[1] Therefore, in spite of its occasional toxicity cinchophen has been used by those of greatest experience with gout; many [310, 690b] in America still prescribe it to be used intermittently for long periods somewhat after the plan of Graham (1920; 1926).

Graham's present method [272] of using cinchophen to prevent attacks follows: Cinchophen 15 grains t.i.d. first day of week, no medicines on second day, acetylsalicylic acid grains 10 t.i.d. on third to sixth day of week if pain persists, no medicine on seventh day; this weekly program to be continued indefinitely. To test a patient's tolerance to cinchophen Graham recommended for the first week one 15 grain dose only; for the second week two such doses; the third week three such doses one day a week. If hyperuricemia persists, cinchophen is given two days a week, 15 grains t.i.d. After severe attacks or in recurrent cases "cinchophen should be given for many months." Blood uric acid should be estimated every one or two months; if it approaches normal the dose of the drug is reduced or stopped temporarily.

Some patients fear, others do not well tolerate, cinchophen; others with hepatic dysfunction should avoid it. For such patients, unable to prevent acute recurrences by diet alone, Hench prescribed salicylates (60 grains) with (glycine) amino-acetic acid (150 grains) daily during attacks and intermittently thereafter. A synergistic action of salicylates and glycine was noted in normal persons by Quick (1933). This seemed to control symptoms and hyperuricemia in the case of Rutledge and Bedard.

[Hench's preliminary results with these drugs seem to indicate that they are effective both clinically and chemically in some cases, clinically (providing analgesia) but not chemically in others, chemically (controlling hyperuricemia) but not clinically in others. This is probably as should be expected for "hyperuricemia" and the disease "gout" are not synonymous. Its further use is justified but it is not a complete substitute for cinchophen.—Ed.]

According to Jennings salicylates alone (80 grains daily) are quite as effective as cinchophen (45 grains daily) in controlling pain and hyperuricemia. Their effects were studied in eight cases: two males with tophi, three males and three females with pretophaceous gout. [The presence of gout in two of the females seems debatable.—Ed.] Augmentation of urate excretion was actually somewhat greater from salicylates in six cases, from cinchophen in one case; one case was equally affected by both drugs. The total average daily urate excretion in the eight cases was 0.37 gm. without drugs, 0.52 gm. after atophan, 0.66 gm. after sodium salicylate. In two cases the blood urates were unaffected by atophan; otherwise both drugs consistently lowered blood uric acid. The total average blood uric acid concentration for the eight cases was 4.4 mg. per 100 c.c. before atophan, 3.1 mg. after atophan; 5.1 mg. before salicylates, 2.6 mg. after salicylates. The height of blood uric acid before use of a drug bore no fixed relationship to the amount of uric acid excreted after use of the drug or to the drop in the level of blood uric acid during its use; urinary urates were far in excess of amounts lost by blood; hence, much of the urates excreted under the

influence of these drugs must come from tissues, including tophaceous deposits. Jennings recommended prophylactic therapy to include sodium salicylate 80 grains daily, sodium bicarbonate 120 to 150 grains daily three to four days a week; it will control hyperuricemia and is free from serious toxicity.

Cinchophen Toxicity. Cinchophen was considered "a very important drug for which there is no substitute," [636] "practically specific in many cases of chronic gout," [148] "of great value between acute attacks of gout," [374] "the most valuable in preventing attacks of gout and alleviating the chronic joint condition." [272] But it was also considered a dangerous drug, to be used with caution. [Some of us do not believe there is any method of giving cinchophen "with caution" since severe toxicity may result occasionally from small doses.—Ed.] Kersley noted "transitory jaundice" from one dose (7½ grains) given for an unstated disease (gout ?).

[It would be interesting to know this point because cinchophen toxicity has rarely been noted in gouty patients; there were only six cases of "gout" among the 191 cases of cinchophen toxicity reviewed by Palmer and Woodall, 1936.—Ed.]

Hench quoted the statistics of Bryce: The chances of fatal toxicity from cinchophen are about one in each 61,000 courses of treatment, a "typical course" being the use of ¼ pound (0.1 kg.) per patient. Since statistics indicate that in uncontrolled gout the chances of gouty nephritis or other serious complications are at least 15 per cent or more, certain American students of gout [but not all.—Ed.] have felt justified in assuming the small risk from cinchophen to try, if possible, to prevent the serious, even fatal renal or vascular manifestations of gout as well as the progressive disability of gouty arthritis.[310]

[But those who assume the risk must face the facts and if it can be shown that salicylates, with or without amino-acetic acid, will effectively control gout it would be senseless to support the cause of cinchophen longer. One of us, W. B., believes that neither cinchophen nor any other treatment materially alters the course of gout or stops the progression of gouty nephritis once the latter has begun. Others of us believe that, in spite of our inadequate knowledge of gout, an attempt to control the hyperuricemia of gout is sound therapy even though hyperuricemia may be a secondary, not a primary, factor in the disease. However, none of us has final proof for or against these beliefs and further prolonged observations are in order.—Ed.]

Three new cases of cinchophen toxicity were noted: none were cases of gout. A patient with "pain in sacroiliac region for some weeks" took 70 to 80 grains of neo-cinchophen over a period of several days; there ensued marked hepatitis and jaundice (icterus index up to 195, van den Bergh up to 10); under treatment (large amounts of glucose, high carbohydrate diet, "liver poultice") the patient recovered completely.[191] Lyall noted two fatal cases of liver atrophy from atophan; a man with "rheumatism" for six weeks (finger joints stiff and sore) took 18 tablets (size unstated) within 14 days; a woman with "rheumatoid arthritis" for many years took an unstated amount of atophan.

Palmer, Woodall and Wang again reviewed the 191 cases of cinchophen toxicity reported in the literature; there were 88 deaths, mortality rate 47 per cent. In some cases toxicity, occasionally fatal, occurred from very small, carefully administered doses. In some cases the drug was given carefully, fearfully, and its administration was stopped promptly with onset of toxicity, yet death resulted. "This illustrates the futility of attempting to find a safe method of administration and of thinking that the drug can be given safely, if given cautiously, under observation." Often signs of toxicity first appeared long after administration of the drug was stopped. Occasionally it can be taken in rather large doses for a long period without apparent ill effects until suddenly jaundice appears; death may then rapidly ensue. Sex and age were not apparent factors; most patients did not previously have hepatic disease. The long time which may elapse between ingestion of the drug and onset of symptoms "speaks strongly against an allergic basis although the cutaneous reactions which appear promptly do seem to be of this type. It does not seem to be a question of idiosyncrasy but of variable susceptibility." To determine the incidence of toxic hepatitis with and without cinchophen, more than 3000 records of necropsy were reviewed; these included 21 cases of toxic necrosis and cirrhosis of liver, in at least six of which cinchophen had been taken for "arthritis."

In Scotland under the Poison Act (1936) atophan became a "Schedule 1 poison"; Lyall urged government control over all such preparations.

Some have been able, others unable to produce experimentally in animals toxic lesions from cinchophen. After dogs had been given variable doses of cinchophen (1 to 2 gm. daily) by various routes Stalker, Bollman and Mann noted no change in the level of gastric acidity but an increased amount of gastric secretion; this was followed in 96 per cent of animals by the development of ulcers, generally peptic, occasionally duodenal, then gastric hyposecretion. Formation of ulcer was prevented or modified by certain factors enumerated. No definite instances of cinchophen toxicity with ulcer formation have been noted in man.

Psoriasis and Psoriatic Arthritis

The literature on psoriatic arthritis and requirements for its diagnosis were briefly reviewed by Jeghers and Robinson who reported one case and summarized certain clinical characteristics of the disease.

> Features of the case [the patient was a man aged 54 years] follow: psoriasis 15 years without joint lesions; then sudden marked extension of psoriasis with involvement of nails and changes in the character of the cutaneous lesions; malaise, chilliness, weakness, slight fever; a few weeks later onset of severe polyarthritis (knees, elbows, ankles, wrists, hands) which forced the patient to bed; roentgenograms showed periarticular swelling, slight bone atrophy and destruction, findings similar to those of atrophic arthritis. Ignoring the skin, joints were treated vigorously for six weeks without effect; treatment of joints was then abandoned, a diagnosis of psoriatic arthritis was entertained and the skin treated vigorously by Goeckerman's (1931) regimen. Skin and articular lesions cleared "completely" within a few weeks.

Jeghers and Robinson agreed that a diagnosis of true psoriatic arthritis depends mainly on the close relationship which exacerbations and remissions in skin may bear to those in joints. Psoriatic arthritis resembles atrophic arthritis in many ways but possesses certain distinctions: frequency of severe involvement of terminal joints of fingers and toes with psoriasis of adjacent nails (Brocq 1910, Hench 1935); articular remissions which are more frequent, rapid and complete than in ordinary atrophic arthritis and which may occur when skin clears spontaneously or under therapy. However, after several attacks or in severe cases joint lesions may take an independent or resistant course, ending in permanent damage. "The parallelism between the severity of the skin and joint lesions seems to support the theory that the arthritis is due to toxic products absorbed from skin lesions." Cases of psoriatic arthritis are too infrequently recognized: dermatologists tend to ignore the joints; internists ignore the skin. [One of us, W. B., recently noted a case of chronic polyarthritis with psoriasis in which cinchophen toxicity induced a complete remission of the arthritis but not of the psoriasis.—Ed.]

Among 231 cases of psoriasis Lane and Crawford noted 74 (32 per cent) with "arthritis"; of these 14 had "psoriatic arthritis" (simultaneous onset or synchronous aggravation of skin and joint lesions). Characteristic nail changes were present in fingers in half of the cases; in toes in a fourth. In all cases with involvement of toe nails, finger nails were also affected. [No note was made on the terminal phalangeal joints.—Ed.] A variable (generally beneficial) effect of pregnancy on psoriasis was seen. Among 19 cases of "rheumatoid arthritis" in which psoriatic lesions were present Dawson noted seven which some might have called true psoriatic arthritis. Less than 2 per cent of patients with rheumatoid arthritis develop psoriasis. Dawson reached no conclusion as to the validity of the entity. Brief reviews of current theories on causation and methods of treatment of psoriasis were made (without comment on joints) by Orr and by Oliver and Crawford. Some associate psoriasis with faulty lipid metabolism and increases of certain blood fats. Rosen, Rosenfield and Krasnow noted low rather than high values for blood cholesterol, but changes were slight and they could not postulate a disturbance in lipid metabolism in psoriasis.

The preliminary effects on psoriasis of massive doses of vitamin D and ergosterol were noted by Ceder and Zon. Of 15 patients with psoriasis [joints not mentioned] given 300,000 to 400,000 units daily for several (up to 12) weeks, the skin of 11 cleared completely, that of two partially; two patients were not benefited. All developed transient hypercalcemia (12 to 16 mg. per cent); several noted mild, transient toxicity. [May not such degrees of hypercalcemia be potentially dangerous?—Ed.] The treatment was "practical, simple and effective." Colloidal manganese was considered of value by some [505] but not by others.[500] Some recommended autochemotherapy.[30, 350] Intravenous injections of typhoid vaccine are frequently used for psoriasis; such an injection after three preliminary subcutaneous doses

was followed, in a case of Rosen, by an unusual reaction: edema, erythema, renal and hepatic damage; the patient responded to intravenous injections of 10 per cent glucose.

Hemophilia and Hemophilic Arthritis

Brief reviews of current opinions on the pathogenesis and treatment of hemophilia appeared [213, 433, 516, 665] but no new studies on hemophilic arthritis. A few cases of hemophilic arthritis were mentioned.[213, 665] Hemophilia in negroes is extremely rare; three cases, two with typical genealogical charts, were noted by Pachman; one had arthritis.

Although Birch's hypothesis was endorsed by some,[665] Eley considered the theory unproved and ovarian substances of debatable value. Theelin therapy was followed by improvement in one of Pachman's cases. Eley discussed further the value of the anticoagulant extract from human placentas developed by Eley, Green and McKhann (1936). In 12 of 19 hemophilic children, given the extract orally or intramuscularly, normal blood coagulation resulted; a later report noted favorable results in 13 of 20 cases.[212, 213] The effect persists only 48 to 78 hours. Intravenous injections of the extract may prove fatal. In certain cases the extract was valueless. It seemed of value in two of Pachman's cases. Clots formed by this extract in vitro and in vivo were studied.[460] Addition of the extract to plasma of hemophiliacs increased the coagulation time and caused the formation of large, firm, slowly retractile, hydrophilic clots. Hemophilic patients who received the extract orally obtained reduced coagulation time of blood and improved blood clotting but in no instance were clots entirely normal.

Normal, fresh plasma and serum contain a coagulation-promoting substance of uncertain identity; it is present in the protein fraction but is not euglobulin. Bendien and Van Crevald described methods for its separation. It was given intravenously to three hemophilic patients; blood coagulation in one case was repeatedly kept normal for some days. The coagulation defect responsible for hemophilia concerns plasma rather than platelets, according to Patek and Stetson (1936) and Patek and Taylor (1936), who isolated from human plasma a clot-accelerating "globulin substance" "closely similar" to that of Bendien and Crevald; its physicochemical properties were studied further.[526, 549] The substance, injected intramuscularly, markedly reduced coagulation time of hemophiliacs. The first and successful use of maggot therapy for infected wounds of hemophiliacs was reported.[548]

Allergic Arthritis

Little appeared to clarify the term "allergic arthritis" but several writers manifested their receptivity to the idea that offending food or bacterial antigens can produce allergic arthritis in susceptible persons. Ishmael and McBride " found such foods as grapefruit, prunes and coffee to be offending

antigens. As a rule the increased pain, swelling and redness comes on one and one-half to two hours following the ingestion of the food and lasts for about three days. The leukopenic index and intradermal skin tests are used as the laboratory test for sensitivity." Cmunt supported the idea that allergy forms the common basis of several of the rheumatic diseases. He observed a "typical case of allergic arthritis in a patient whose knee was swollen after eating sauerkraut, fruit, buttermilk and yohimbine." To Cmunt gout is also an allergic reaction in persons sensitive to certain foods, not necessarily purines; mentioned was a case of acute gouty arthritis precipitated by milk, but not by ham; another precipitated by gherkins.

[No details concerning these cases were given.—Ed.]

Service saw four patients, each with a family or personal history of nonarticular allergic manifestations who developed idiosyncrasies to food or digestive difficulty and later developed intermittent "hydroarthrosis of allergic origin," relieved by avoidance of offending food antigens.

1. A woman, 34 years old, began at the age of 30 to have, at irregular intervals, pain and stiffness of a shoulder lasting severely three to five days, mildly seven to 10 days more. Association with ingestion of chocolate finally was noticed. Eosinophilia, 6 per cent, was present. [Eosinophilia as high as 15 per cent occasionally accompanies atrophic arthritis.—Ed.] "Food tested," she reacted (skin?) to several foods including chocolate. Avoiding these foods she was free of gastrointestinal symptoms and shoulder pain; eating them she experienced gastric disturbances and "hydrarthrosis," once with special severity within 24 hours after eating large amounts of milk and chocolate. Leukocytes fell from 6800 to 4050. Roentgenograms showed no arthritis.

2. A man, aged 46 years, had "gastrointestinal allergy" for seven years, asthma three years. During severe asthmatic paroxysms he developed tenosynovitis and hydrarthrosis of hands and fingers which persisted a week or more after the asthma subsided. Avoiding foods and epidermals to which he was sensitive he escaped asthma and hydrarthrosis.

3. A woman aged 59 years had hay fever, "gastrointestinal allergy," chronic hypertrophic arthritis of the cervical and thoracic spine and "arthritic changes" of the shoulders and right knee. Avoiding 22 foods to which she was sensitive she noted relief of symptoms in shoulders and neck. Eating citrus fruit caused "an immediate return" of symptoms therein. "Because of the marked limitation of motion as well as pain, a hydrarthrosis was considered to exist in the shoulder region." [Criteria for such a diagnosis were inadequate.—Ed.]

4. A woman aged 58 years with "gastrointestinal allergy" for three years, had hives for three months; shortly thereafter she noted stiff swollen fingers, later painful stiff shoulders. Food tests were negative. Eliminating wheat, beans and potatoes, she was free of pain and swelling in hands and shoulder. The hives persisted "until splenic fluid was given." One of the foods produced definite leukopenia.

[There seems to be no good reason to deny the possibility that in certain cases articular tissues, like so many others, might well react to offending food antigens. Yearly we have briefly described the cases of so-called allergic arthritis to get a more definite picture of the supposed entity but to date no clear syndrome has emerged. No consistent clinical picture has been described; practically no pathologic data have been offered. Case records have been notable for the absence of important details; diagnoses have been based on meager clinical evidence incriminating certain foods, on

skin tests and leukopenic indexes which are generally regarded as of doubtful significance and, most important, on supposedly positive therapeutic tests. The latter would be much more significant were it not that spontaneous remissions are so common in all arthritides. Current reports do little to clarify the syndrome; the cases noted above were certainly not of true intermittent hydrarthrosis. Those who recognize "allergic arthritis" from foods may have the right idea but they are urged to present more comprehensive studies on the clinical and pathologic aspects of the supposed entity and particularly to make more rigorous and prolonged observations on therapeutic and provocative tests.—Ed.]

Metabolic Arthritis

Incapable of accurate definition, this term was avoided almost completely in the year's literature. We would agree with the remark: "Metabolic disturbances as a cause of rheumatism are in a very uncertain position." [552] As noted in previous Reviews those who advocate the use of sulfur for atrophic and hypertrophic arthritis consider these diseases due to a disturbance in sulfur metabolism, hence examples of "metabolic arthritis." A supposed example of "metabolic arthritis" was reported by Engel: the case of a child first seen at the age of three years suffering from recurrent arthritis of a hip and acetonemic, cyclic vomiting. Four spells of coxitis were separated by normal intervals of several months; each coxitic spell ended in the course of a severe attack of acetonemic vomiting, which suggested to Engel that the acetonemia was not caused by the arthritis but was a primary feature. The patient had no attacks in 14 years. Seen again at the end of that time, the head of one femur was thickened and the neck shortened. The question was raised whether toxic substances (acetone, aceto-acetic acid, etc.), prevalent in recurring vomiting, may have had an elective affinity for articular cartilage similar to that of homogentisic acid in ochronosis (alkaptonuria).

[The significance of this interesting case is difficult to interpret. One cannot be certain which preceded—the coxitis or the acetonemia.—Ed.]

Endocrine Arthritis

Menopause Arthritis. Endocrine, climacteric or menopause arthritis occasionally was mentioned in the usual vague manner. Some considered menopause arthritis synonymous with hypertrophic arthritis; others considered it a separate disease, with distinctive features in its early stage but later indistinguishable from hypertrophic arthritis. Without committing himself to details, McConkey considered abnormal endocrine function, especially of adrenals and thyroid, a fundamental factor in the causation of chronic, especially hypertrophic, arthritis. According to White "climacteric arthritis" results from endocrine changes occurring in women at the menopause, resembles hypothyroidism in its early stages and is indistinguishable from osteo-arthritis in its later stages. Without clinical definition, Hartfall, Garland and Goldie noted the effects of chrysotherapy in 23 pa-

tients with "chronic villous arthritis (climacteric or menopausal)" aged 40 to 66 years with erythrocyte sedimentation rates more than 10 mm. (1 hour) in only seven cases; improvement was marked in seven, moderate in seven, insignificant in nine cases.

Symptoms and treatment of "menopause arthritis" were reviewed by Holmes, who defined it as an arthritis occurring only in women and "commencing within the five or six years preceding or following cessation of menstruation." About the age of 50 years, patients noted insidious onset of aching stiffness, especially of knees and fingers. Affected persons were well nourished, slightly obese, not toxemic. They experienced discomfort when descending stairs, walking, or rising from chairs. Aside from joints, physical signs were "mainly those of thyroid deficiency (although it was stated that low metabolic rates were uncommon) ranging from small localized patches of indurated fibrous tissue to well-defined myxedema." Knees in the early stage are characterized by chronic synovitis: tenderness, thick synovial membrane, crunching sensations, little or no hydrops, no muscle atrophy. Roentgenograms then are negative. Later "the disease closely resembles osteo-arthritis, from which if left untreated it is almost indistinguishable." In hands carpometacarpal and terminal phalangeal joints are generally affected, occasionally wrists. Tender periarticular infiltrations affect the terminal joints; later they ossify as Heberden's nodes. Original studies on articular pathology were not mentioned but the writer's colleague, Franklin, about 1912, did "limited synovectomy" in six or seven such cases and noted "villous synovitis": "The villi were just hyperemic, edematous synovial membrane"; in no case was there any bony change; when the latter occurred it "indicated a change of the pathology—osteo-arthritis supervening on an old menopausal joint."

[Surely this describes nothing more nor less than "the pre-roentgenographic phase" of hypertrophic arthritis. There seems to be no evidence offered to justify recognition of menopausal arthritis as a separate entity. It is to be regretted that current writers on "menopausal arthritis" can either present no data on its pathologic reactions or must rely on a brief study 25 years old, rather than presenting studies based on the newer knowledge of articular pathology. The latter might quickly settle the issue.—Ed.]

Early and appropriate treatment will bring about complete cure in the majority of cases, or at least will arrest the disease before crippling ensues, according to Holmes, who prescribed removal of obvious septic foci, correction of constipation, a diet low in carbohydrates and calories but rich in vitamins, reduction of trauma, moderate exercise, analgesics, iodine, thyroid at times, physical therapy and estrogenic hormone, 1000 to 10,000 international units injected every other day.

[Estrogenic hormone, at current prices, would cost $0.50 to $1.50 a daily dose, a price prohibitive to most patients even were the substance of assured value for joints. In some preparations 1 rat unit equals approximately 5 international units. —Ed.]

According to Miller, "menopause arthritis would be best described as osteoarthritis from the trauma of obesity occurring at the menopause." In conclusion we would agree with O'Reilly: "At a time when aging bacteriology is being deserted for the fresher promises of the endocrines, an undue significance may be paid to [endocrine arthritis.] It is well to note that there is little evidence of endocrine disturbance in [patients with hypertrophic arthritis,] nor in the acknowledged endocrine disorders is there any constant association with arthritis."

Arthritis and the Parathyroids. Ankylosing arthritis is no longer considered a manifestation of hyperparathyroidism. To date there have been reported at least 145 proved cases of the latter. All were reviewed by Jacobs and Bisgard: in many cases the skeletal symptoms—backache, leg pains, etc.—had been called "rheumatism" or "arthritis," but no proved case was accompanied by ankylosing arthritis. Furthermore no cases of ankylosing arthritis exhibit the chemical features distinctive of proved hyperparathyroidism. To avoid diagnostic errors, physicians should be familiar with the classical features of clinical and experimental hyperparathyroidism. They have been discussed in previous Reviews: several excellent new reports may be consulted.[11, 12, 97, 117, 118, 227, 339, 343, 680]

Miscellaneous Types of Joint Disease

Intermittent Hydrarthrosis. In 1929, Weissman-Netter proposed the use of ergotamine tartrate for this condition. By this method Cook apparently stopped the disease in one case.

> In 1932 a man, aged 43 years, had had attacks in a knee for 15 years every 21 days (attack five to six days; free interval 15 to 16 days). One tablet of ergotamine tartrate (gynergen, 1 mg.) was given daily for two weeks; then a mild attack lasted two days; one tablet was taken daily for seven weeks with no attacks. Treatment was omitted for one month; an attack ensued. One tablet was given every other day for two months; no attack occurred. Treatment was again stopped for two months; one attack occurred. Gynergen was taken daily for one month; then every other day for six weeks; there was no attack. Between November 1933 and November 1934 one tablet was taken twice a week except for two periods of six weeks each; only during these periods were there (two mild) attacks. Since November 1934 no medicine was taken and attacks have not recurred.

The cause of several recent cases of intermittent hydrarthrosis has been found to be undulant fever.[4, 40] [In our experience most cases of irregularly recurring "intermittent hydrarthrosis" eventually prove to be cases of atrophic arthritis. —Ed.]

Suppurative Tenosynovitis. Grennell summarized data on 125 cases in which hands were affected: 67 of the "primary type" (infection implanted directly into the sheath by injury; generally puncture wounds); 58 of the "secondary type" (sheath involved by extension of adjacent infection); none were hematogenous. Flexor finger creases and distal closed spaces were most often affected. Results of surgical drainage were poor; complete or nearly complete function was restored in only 17 per cent of cases. Gross

tendon necrosis occurred in 52 per cent. Recovered at operation were hemolytic streptococci in 36 per cent, staphylococci in 31 per cent (patients so infected responded best); mixed organisms in others (these did poorly). Suppurative arthritis, especially of a distal phalangeal joint, and osteomyelitis were frequent complications. Delays in operation due to errors in diagnosis were frequent and an important factor in the poor results.

[This frank appraisal of the difficulties encountered is commendable.—Ed.]

Peritendonitis Crepitans; Crepitating Tenosynovitis. Howard studied 32 cases of this disease, a traumatic tenosynovitis from acute accidental or chronic occupational trauma. Aching, soreness, local warmth, swelling, redness, often edema affect a particular muscle group in arm or leg. One can feel, and with a stethoscope hear, a distinct and often loud, crackling crepitus. Parts affected are tendons generally at or near the musculotendinous junction, "never in that part of the tendon supplied with a synovial sheath." Radiocarpal extensions are most often involved. Interstitial deposits of masses and clumps of fibrin produce the crepitation. The pathologic changes in three cases were described. Heat, massage and exercises are usually advocated but merely prolong disability; rest and complete immobilization for a few days are required.

Synovioma. Synoviomas are benign or malignant. The latter are rare and of rather recent identity (described by Langenbeck, 1865, named by Smith, 1927). Coley and Pierson reviewed the 20 cases in the literature and added 15 more seen by them since 1900. Synoviomas arise from synovial membrane within joints, from bursae or from pouches or prolongations of joints and may involve connective tissue, tendon sheaths and lymphatic structures. They produce symptoms simulating those of the common articular diseases. After excision they tend to recur and often metastasize to lungs. Joint function is often little impaired. Bone is generally unaffected; hence roentgenograms may be negative unless attention is paid to soft tissue detail. As there may be no palpable tumor, diagnosis often is difficult; it usually is made on exploration, generally of a knee, sometimes of a finger, ankle, metatarsus, hip, elbow or shoulder. Adenopathy rarely occurs. Conservative treatment is inadequate. The tumors are "radioresistant." Statistics on end results indicate that previous treatments generally have been too conservative. Of the total 35 patients, none survived more than 10 years; six have lived five years; 13 have lived three years; many died within two to five years. Amputation was recommended unless wide excision is still practicable.

Chondromatosis. True chondromatosis is rare; most cases so called are examples of hypertrophic arthritis. Only three proved cases were found in the rich material of the orthopedic department of the State University of Iowa. Freund reported them: one in which a shoulder was affected; two, a hip. In one case locking of a hip occurred; the femoral head had been forced almost out of the acetabulum, yet roentgenograms were negative. At

operation, 395 free joint bodies were found. Chondromatosis does not represent a blastomatous change of synovial membrane, according to Freund, but a metaplastic hyperplasia of connective tissue similar to that of myositis ossificans. Supporting this idea is the close embryonal relation of synovia to cartilage (which explains the prevalence of cartilaginous tissue in the disease), and the occasional spontaneous resorption of calcified bodies.

Ganglia and Synovial Cysts. Whether ganglia and synovial cysts are slightly different modifications of the same condition never has been determined; clinical distinction between them is often impossible. According to Jensen, their morphology and pathology are essentially the same and they are similar to bursal hygromas. [One of us, J. A. K., does not agree.—Ed.] However, the latter differ from the former in that they have useful function; in ganglia and synovial cysts the bursal functional aim is absent. Theories on the origin of ganglia and synovial cysts were reviewed. Jensen concluded that they originate from embryologic arrests in the process of the development of periarticular tissues and synovial membranes, and have little or no relation to trauma. Jensen presented clinical and pathologic data on 21 simple cystomas (generally affecting wrists, occasionally fingers; essentially symptomless) and 23 cysts with pain and some limitation of motion. A few of the latter were tuberculous. From their study of 50 cases of ganglion, De Orsay, Mecray and Ferguson concluded that trauma is a definite etiologic agent and that the masses arise from degenerations of mesoblastic tissue. They appear first as solid masses; small cysts later form and coalesce as large cysts by disappearance of intercystic septa. Contents were believed to be myxoid, not mucinous; hence the process is one of degeneration of collagen fibers rather than a secretion of connective tissue cells.

Treatment by sclerosing solutions effects cures occasionally. Permanent cures can be expected in about 50 per cent of cases by simple rupture and dispersion; in about 85 per cent by excision. Recurrences result from continuation of the degenerative process in tissues adjacent to the original ganglion [187]; hence all tissue undergoing myxoid degeneration should be removed by fairly wide excision of tissue.

Hypertrophic Pulmonary Osteo-Arthropathy. Three reports on this condition appeared; theories on etiology and pathogenesis were reviewed but no new data thereon were offered. Pulmonary neoplasms were the basis of Craig's four cases: three were at first called "rheumatoid arthritis"; one, "acromegaly." Causes in Cushing's five cases of clubbed fingers and osteoarthropathy were lung abscess, empyema, bronchiectasis, congenital heart disease, biliary cirrhosis. Kennedy noted a case in which the patient was a boy, seven and one-half months old—the youngest patient so far encountered. At the age of three weeks a series of infections began, including multiple lung abscesses with enlarged liver and spleen at five months. Death occurred six weeks after rib resection; detailed necropsy data were given.

Scleroderma. Periarticular tissues of fingers and toes are frequently affected in scleroderma; patients so affected often complain of "rheuma-

tism," phalanges being puffy, stiff, sometimes painful. Calcium metabolism in scleroderma was studied by Cornbleet and Struck, who could find no evidence of parathyroid dysfunction but noted retention of calcium and phosphorus in the body, excretion of only small amounts in urine. Large daily doses (200,000 to 300,000 international units) of vitamin D seemed of benefit; this increased urinary calcium and provoked a loss of calcium and phosphorus from the body. Eleven patients were treated: at least four months of treatment were required for improvement. An hypothesis was offered: Scleroderma is initially due to a toxin which injures the collagen syncytium; these injured tissues secondarily take up calcium, thus accounting for the frequently observed positive balance in the disease. Massive doses of vitamin D produce a negative balance, apparently at the expense of calcium deposited in collagen and muscle. [Were this theory correct would not the use of parathormone be more effective and perhaps safer? However, it is difficult with any decalcifying agent to remove calcium and phosphorus from soft tissues.—Ed.]

Malignant Lymphoma with Articular Symptoms. Rheumatic types of pain may be the only early symptoms of the leukemias with lymphomas; Floyd noted six such cases among children. They complained of pain in various joints often long before changes in blood or lymph nodes were noted. Diagnoses made by biopsy were as follows: malignant lymphoma in one case, lymphatic leukemia in two, myelogenous leukemia in two, Hodgkin's disease in one. Severe anemia, much more profound than that in atrophic arthritis, was present in all.

Calcium Deposits about Joints. Calcium deposits " exactly similar " to those frequently present about the shoulder (in supraspinatus muscle, articular capsule, or subdeltoid bursa) were found by Hitchcock about various joints—hip, knee, ankle, elbow, wrist, metacarpal and phalangeal. They may be symptomless or associated with acute or chronic inflammation, at times severe pain, redness, swelling, fever. Reports of nine cases were given. Occasionally trauma was an obvious cause; in other cases a history of trauma was absent. There was no evidence of metabolic derangement or infection; cultures of tissues and animal inoculations gave negative results. Hitchcock advised surgical evacuation of the deposits. On incision, a greasy, mortar-like calcium paste was found in a tense sac with inflamed tissues about it, and within the sac necrotic tendon or connective tissue. Postoperative convalescence usually was uneventful. If incision is not made, the inflammatory hyperemia may be sufficient to cause absorption of the calcium and lead to self-cure, but this may take several painful weeks. Diathermy treatments seemed to promote absorption and healing in some cases.

De Lorimier studied effects of roentgenotherapy on 31 cases of " paraarthritis " with 48 calcareous deposits in the following tendons: supraspinatus 20 times, infraspinatus 11, teres minor three, triceps brachii one, pyriformis six, gluteus medius one, obturator internus three, adductor

magnus one, flexor digitorum one, flexor hallucis one. Calcareous deposits about a shoulder were generally not in the subacromial bursa but in any one of several tendons: supraspinatus, infraspinatus, teres minor, triceps brachii. Some deposits were painless and found accidentally; others were associated with symptoms of acute or chronic "para-arthritis." Results of roentgenotherapy follow: Symptomless calcareous deposits were not absorbed; in cases in which symptoms were mild or moderate, there was complete or marked calcareous absorption and relief of pain; in cases with very acute pain, results were best—marked relief of pain and rapid absorption of deposits. Since irradiation had no effect on symptomless deposits, obviously results are not affected by irradiation alone; irradiation probably initiates an inflammatory reaction which somehow contributes to the "absorption potential" and affords most effective relief of pain.

[When seen surgically these deposits are described as "mortar-like," "creamy," or "tooth-paste-like" deposits of calcium; they are not bone. As will be noted under comments on subacromial bursitis, when marked hyperemia is present deposits may rapidly disappear spontaneously. Simple immobilization of a shoulder for 24 hours may markedly relieve pain and muscle spasm in acute cases. How effective or superior roentgenotherapy really is remains for further studies to determine. It would have been of interest had De Lorimier treated a control series otherwise than by roentgenotherapy—by measures hereinafter noted.—Ed.]

Ehlers-Danlos Syndrome. Features of this syndrome include: (1) hyperelasticity of skin; (2) friability of skin and its blood vessels, resulting in formation of papyraceous scars, e.g. about knees; (3) "looseness" or hyperextensibility of joints, particularly of fingers and thumbs. In some cases cystic, subcutaneous nodules are present. Three cases with striking familial features were noted by Stuart; seven cases by Weber. The syndrome may represent a congenital developmental mesenchymal dysplasia.

[Joints were apparently symptomless.—Ed.]

Juxta-articular Adiposis Dolorosa. Obese multiparas past middle age are prone to have painful masses of fat near joints, especially over the medial aspects of knees and elbows and lateral aspects of ankles and hips. Kling carefully analyzed many aspects of this syndrome as seen in 125 cases. It almost never affects males. In women it occurs at the time of the menopause. Blood counts were normal; sedimentation rates were normal in a third, moderately elevated in the rest. In a third the basal metabolism was slightly subnormal. Blood calcium was normal; blood cholesterol of 14 of 16 patients examined was increased. Symptoms included pain, weakness, stiffness, coldness and paresthesia of extremities. Pathologic reactions in biopsied tissues were minimal. The condition was often associated, causally according to Kling, with hypertrophic arthritis. Various treatments were valueless. The condition may represent the early stages of true Dercum's disease. Other theories were discussed.

[This is a thorough study of a subject about which little is known.—Ed.]

Diseases of Muscles and Fibrous Tissues

Rupture of Muscles and Related Tissues. Ruptures of muscles and tendons are common injuries but are often misdiagnosed and treated for arthritis, bursitis or sprain. Ruptures most frequently afflict physically active middle-aged persons whose age has reduced their tolerance for stress and strain. Conwell and Alldredge listed the factors which predispose to rupture: senility, various diseases (arthritis, myositis, acute infectious disease, arteriosclerosis, syphilis, tuberculosis, neoplasm), physiologic predisposition, occupation and fatigue. Disease definitely is a predisposing factor but is not necessary. Ruptures may affect many muscles, most commonly those of the calf, extensors of the leg, biceps, Achilles tendon, extensor of the thumb; less frequently supraspinatus, rectus abdominis, extensors of the fingers, adductors of the thigh and triceps. Signs and symptoms peculiar to rupture in these various regions were illustrated in case reports by Conwell and Alldredge and by Compere and Siegling; the latter in particular discussed traumatic affections of the extensor apparatus of the knees. Examination should be made for localized pain, loss of function or painful function of a muscle or, particularly, a defect or hollow in a muscle or tendon. Roentgenograms of soft tissues may be helpful in diagnosis. Early diagnosis and treatment may prevent prolonged disability. Individualized treatment is necessary: Complete ruptures generally should be sutured; partial ruptures may heal during immobilization.

Classification of Diseases of Muscles. Omitting traumatic lesions, Slocumb classified muscle diseases thus:

I. Parenchymatous myositis
  A. Suppurative myositis
    1. Primary suppurative myositis
    2. Secondary suppurative myositis
  B. Nonsuppurative myositis
    1. Dermatomyositis
    2. Primary myositis fibrosa
    3. Trichinous myositis
II. Myopathies (primary diseases of muscles, secondary changes in the somatic nervous system)
III. Interstitial myositis
  A. Myositis ossificans
    1. Progressiva
    2. Traumatica
    3. Circumscripta
  B. Intramuscular fibrositis ("muscular rheumatism")
    1. Primary intramuscular fibrositis (muscular rheumatism, lumbago, torticollis), a disease unaccompanied by, and independent of, any other recognized disease

2. Secondary intramuscular fibrositis (involvement of muscles and fibrous tissue in various diseases: rheumatic fever, gonorrhea, gout, influenza, etc.)

Commonest of all these diseases is muscular rheumatism, acute or chronic, unaccompanied by other diseases. Because pathologically muscular rheumatism is accompanied by no significant parenchymatous lesion, no true myositis or affection of muscle cells, but at times reveals minor, but none the less significant, lesions in interstitial tissue of muscles, many consider the term "fibrositis" more correct than "myositis." True myositis actually is rare.

Fibrositis

The different anatomic forms of fibrositis, symptoms peculiar to each form, their supposed etiology and their treatment were again discussed by several writers.[22, 84, 88, 121, 147, 240, 263, 264, 338, 395, 627, 683, 720] Reviews of the subject were made by Buckley, Fletcher, Krusen and Slocumb. Fibrositis is of course not confined to intramuscular fibrous tissue but can involve fibrous tissue anywhere.

Primary Fibrositis (Intramuscular; Periarticular). Clinical characteristics of the acute and chronic phases of intramuscular and periarticular fibrositis were described.[22, 88, 147, 240, 264, 338, 627, 683] According to some, physicians too often mistake periarticular fibrositis for atrophic arthritis or for psychalgia affecting joints; patients are either overtreated and given the prognosis of arthritis, or they are undertreated and handled as neurotics. The incidence of periarticular fibrositis is not widely appreciated. During two years Traeger recorded 900 admissions to the arthritis clinic of the Hospital for Ruptured and Crippled, New York City. Among them were 262 patients with stiff, painful, aching joints (not confined to weight bearing regions), worse after rest, better after exercise; most of them were referred as "arthritics"; 128 had symptoms less than two years, 134 had symptoms two to 18 years, yet in none of them were discovered any objective, including roentgenographic or laboratory (for instance, sedimentation rates) abnormalities. Obviously they were not cases of atrophic or hypertrophic arthritis. For reasons given the diagnosis of periarticular fibrositis was made.

Pathology. No new data on pathology were reported. As always, most writers quoted Stockman's findings (1920) rather than their own. The common understanding was that the acute stage consists of edema of low grade with serofibrinous exudate, a slight nonpolymorphonuclear cellular reaction; features of the chronic stage are new fibrous tissue lying in an amorphous serofibrinous matrix, few fibroblasts, no leukocytic reaction, thickening in and around small blood vessels, and the formation of tender fibrous indurations or nodules of varying sizes and shapes.[22, 147, 240, 264] [Two of us, W. B. and M. H. D., cannot accept this description of so-called fibrositic nodules and doubt their existence. Should such exist it is difficult to believe that

simple massage could make them disappear.—Ed.] In Fletcher's experience the structure of the nodule is not typical and apparently consists of "fibrous tissue showing evidences of inflammation and degeneration." Traeger found nodules in a minor percentage of cases. Others [264] insist they are practically always present, their discovery being a matter of "patience and practice." According to some (Clayton and Livingstone): "It often takes five minutes of careful kneading to localize the tender nodules and, unless these are accurately localized treatment cannot be efficient. The average practitioner would never pronounce lungs normal without an examination of at least three minutes, yet few will spend the same time in examining for fibrositis." With increasing experience Krusen found nodules with great frequency: "They are not easy for the novice to find"; 50 per cent of the nodules in Krusen's cases were painless.

Etiology. Previous ideas were restated. Precipitating factors in Traeger's cases were chills, fatigue, trauma, chronic strain, nervous exhaustion, influenza, respiratory and other infections. The usual hypotheses on causation were entertained: The disease probably represents a tissue reaction to bacterial or metabolic (chemical) toxins.[88, 147, 264] Buckley and Gordon considered metabolic toxins the more likely cause. According to Gordon two chief factors operate: mild hypothyroidism and an imbalance in the autonomic system, with consequent inefficiency of circulation and elimination. These lead to accumulations of metabolites in the least vascular tissues of the body; i.e., fibrous tissue.

[These are but speculations; the cause or causes of the disease are unknown. No studies on metabolic rates were currently noted; no conclusive evidence has ever been given to prove that hypothyroidism is a consistent or even a frequent feature of fibrositis, or that body tissues or fluids contain excesses of the known metabolites. —Ed.]

Treatment. Again no new data were given. The usual measures were advocated: in acute cases, rest in bed, a saline purge, acetylsalicylic acid (15 grains every four hours,[240] heat, counter irritants (dry cupping, acupuncture [121]), carefully selected physical therapy, sometimes injections of procaine. Treatment of chronic fibrositis included rest from irritating trauma, removal of foci, a trial of typhoid vaccine or desensitization with some streptococcal vaccine, physical therapy, above all eradication of painful fibrous indurations by firm massage. "Discover the nodule and rub it away" was the universal admonition.[264] Many warned that "this is a painful business." [140, 240, 261] The treatment is "painful and unfortunately not likely to be of much value unless it is" (Fletcher). "Massage must be deep and will therefore be painful"; the fibrous nodules must be "thoroughly broken up" (Copeman). Although painful, treatment must be kept up progressively, effective treatment is somewhat exhausting and only a few nodules should be treated at a time.[240] In some cases, massage should be given only two or three times a week because one may be "stirring up toxins" [720]; heat can be applied daily. Most patients obtain some relief

from heat but some are not "heat-lovers"; they cannot stand heat in any form as it aggravates their pain.[664] General principles and methods of physical therapy for the disease, especially the nodules, were described.[88, 264, 395] Painless nodules should be left alone. Admitting that he was able to relieve many patients by the physical methods described and that massage often causes disappearance of the nodules, pain, tenderness and stiffness, Krusen nevertheless added: "One is still led to wonder whether these nodules are as important as many writers believe and whether they can be 'rubbed away' as consistently as some state."

Vaccines and removal of foci were generally disappointing to Gordon who, on the basis of his concept of the disease, recommended thyroid extract, atropine, ephedrine and hyoscine. No relief should be expected from sulfanilamide.[714] Gold is useless and may be harmful.[147] Skin should be subjected to a "hardening process"—ultraviolet ray therapy and friction baths.[22] [In chronic cases treatment in our experience is often disappointing.—Ed.]

"Senescent Fibrositis." According to Gordon[84] and others fibrositis accompanies every case of osteo-arthritis; indeed the patient's discomfort is often due to the fibrositis more than to the arthritis. Previously this form of fibrositis usually has not been separated from "primary fibrositis" but current writers are speaking more of "senile," "senescent" or "degenerative" fibrositis.[84, 147, 683] Copeman regarded senile fibrositis worthy of separate identity for it is much more resistant to treatment than is ordinary fibrositis. Buckley[84] spoke of "degenerative fibrositis." "Nodule formation is not conspicuous in the fibrositis of this degenerative type, which is more generalized. The process tends to become a fibrosis, a characteristic of senescence." According to Buckley, "The fibrositis of advancing years is due to the action of metabolic toxins such as uric acid, and other products of disordered metabolism and tissue breakdown, and not to bacterial products as a rule. Accumulation of lactic acid, the product of muscular activity, may also act as an irritant." Again, it was Buckley's[86] opinion that gout, or at least hyperuricemia (uric acid more than 3.7 mg. in men; more than 3.5 mg. in females) is frequently associated with attacks of fibrositis which may be chronic in onset and course and not acute, as are the ordinary features of the disease. Indeed, he regarded gouty fibrositis more common than gouty arthritis.

[Few American physicians agree with this concept or would consider chronic fibrositis a manifestation of gout. If gout were found to be the basis of any case of fibrositis that case should be labelled, not "primary" fibrositis, but "gouty" fibrositis.—Ed.]

Comment. [Too many physicians welcome the term "fibrositis" as a convenient scrapbasket into which to discard cases of varied vague aches and pains. Those who erroneously consider intramuscular fibrositis as equivalent to myalgia, and periarticular fibrositis as synonymous with arthralgia, will adulterate their groups of fibrositis with cases of joint and muscle pains due to postural strain, thyroid deficiency, menopause, fatigue, etc. Such physicians make the diagnosis of fibrositis much too often. Other physicians, seeing the term used as a catch-all,

refuse to accept the entity and never make such a diagnosis. In the present state of knowledge no one can say how right or how wrong either group is but they are probably both wrong.

Although of necessity current comments on etiology and pathology of fibrositis are vague, several of the reports noted include clear clinical descriptions of primary fibrositis and its differentiation from the "algias." Physicians would do well to read them sympathetically because in every country there are huge armies of persons who might be said to be "rheumatic" (in the common sense, not in that of rheumatic fever), but not "arthritic," who ache and get stiff but don't swell or get deformed, of persons whose skeletal system is constantly at the mercy of barometric change, shifting winds and air-conditioning. Symptoms are not confined to joints under postural or occupational strain. Although their disease may make them irritable and nervous, they are not true or primary neurotics. Assuredly they are not arthritics, not even "early arthritics," because long observation reveals the persistent absence of objective, roentgenographic or chemical abnormalities (except nodules if and when discovered). Although the term "fibrositis" may seem vague to some and the syndrome it implies incompletely understood, application of this term (or one more suitable) to the cases described herein seems in order. To file these cases away to be forgotten without even a tentative designation is to bury one's head in the sand, and will not help to settle the issue. But to adulterate the syndrome with an array of "algias" will help to perpetuate confusion. What is needed most of all is a comprehensive clinical and pathologic study of the various types of fibrositis. Assuredly the chronic, secondary fibrositis of atrophic arthritis with its muscle atrophy, the acute secondary fibrositis of rheumatic fever, the "fibrositis of gout" (if there is such a disease) should be expected on careful study to reveal pathologic reactions distinct from those of primary intramuscular fibrositis in which significant atrophy rarely, if ever, occurs. If there is a difference between ordinary primary fibrositis and senescent fibrositis studies on pathology should be helpful. But as a basis for these studies information should be obtained regarding the progressive intramuscular changes incident to each decade in the lives of persons without muscle symptoms.—Ed.]

Pharmaceutic Myalgias

Bach briefly reminded physicians of "rheumatism from chemotherapy"; expressions of idiosyncrasy from arsenic, bismuth, mercury, gold, barbiturates, chloral, atophan or antipyrin.

"Psychoneurotic Rheumatism"

To conscientious physicians harassed by doubt whether to classify a given case as one of fibrositis, myositis, postural fatigue or neurosis is recommended Halliday's "preliminary report" on psychologic factors in rheumatism. It cannot be reviewed adequately here but it is a worthy attempt to explain the pathogenesis of "psychoneurotic rheumatism."

The rôle of psychologic factors in producing pain, tenderness and stiffness in various muscles and joints was discussed. Such symptoms, unassociated with organic changes, often are erroneously labelled "rheumatism," "fibrositis," "neuritis," "sciatica," "lumbago," "myodynia"—labels which are "convenient, comprehensive, scientifically vague." But they are in fact symptoms of a chronic psychoneurotic anxiety state in which the "rheumatism" is but an episode. Representative cases were described. Emotion involves the primitive brain, autonomic nervous system, and endocrine glands. Acting through these structures emotional or psychologic

factors may profoundly affect bodily chemistry, rhythm, secretion and even structure. When a person is grieved by the loss of a beloved person or object, between paroxysms of grief he may actually feel sore and stiff as if he had been thrashed. As time passes these bodily reactions usually subside; sometimes they persist in their original or in a modified form. The acute emotional loss of appetite may merge into chronic anorexia, regurgitation, vomiting; the pain of a "broken heart" may persist as precordial soreness or neurocirculatory disorder; in the locomotor system soreness and stiffness and the heaviness of grief may merge into a fatiguing "rheumatism." Thereafter the victim's attention is no longer focused on his grief but is dominated by the physical expression of grief which he henceforth interprets as evidence of disease.

Halliday outlined methods for recognizing, investigating and differentiating such cases; also he commented on their interpretation. Pain may be an expression of inferiority; occasionally persons develop pain in structures which are physiologically or anatomically deficient. The pains not only rationalize the inferiority to the victim but also afford an excuse not to use the inferior part. Examples were given where pain and stiffness, especially in back or neck muscles, invoked the mechanism of symbolism (e.g., a case of "symbolic lumbago"); such symptoms are called "body language." Analyzed in detail were 21 cases (eight males, 13 females) of "psychoneurotic rheumatism." Some of the patients were anxious or depressed, but others were detached, placid, cheerful and smiling. Indeed the trouble more frequently affected self-respecting, independent persons. Commonest symptoms were fatigue, weakness, general soreness, palpitation, sleeplessness, but especially pain and stiffness; in three cases actual articular swelling was noted. The translation of psychoneurotic emotionalism into "rheumatism" took from a week to two years after the emotional encounter. Regions affected were neck only in four cases, neck and left arm in seven, left arm alone in six, right arm alone in one case. Halliday stressed the frequent localization in the extreme left aspect of the body, top of the left shoulder and outer aspect of left arm. The 21 records were epitomized: "I experienced misfortune, I took it ill, I felt it sore and stiff."

In Scotland 10 to 12 per cent of all persons incapacitated for work are labelled "rheumatic." In two series of such cases Halliday found that 39 per cent (of 145 "rheumatic" cases) and 37 per cent (of 62 cases) were pure examples of psychoneurotic rheumatism. Most of these patients are treated by physical means to rub away their pain and stiffness. This treatment usually is contraindicated as it only serves to fix the disease more firmly. These patients must be handled in a special way. They "love" a variety of treatments; they may improve temporarily under sympathetic hospital care but they continue to be ill because of the future more than the past. "Many patients are not prepared to take the consequences of becoming well."

Epidemic Myalgia or Pleurodynia

Features of two or three epidemics were reported. Symptoms were as outlined in last year's Review.[4] Pickles studied 31 cases among children and young adults in 1933 in England. The characteristic paroxysmal thoracic or abdominal pains, with fever and rapid, shallow respirations, were noted. Patients recovered quickly without sequelae; it was intimated that their main danger was that they might fall into the hands of surgeons and be operated on for acute abdominal disease. The general absence of cough and of vomiting were points suggesting the absence of pneumonia or appendicitis. Further studies on the Cincinnati epidemic of 1935 were reported: 282 patients were affected (Harder 1936); among these were 70 children,

studied by MacDonald, Hewell and Cooper. There was abdominal pain alone in 41, abdominal and thoracic pain in 14, thoracic pain alone in seven, and "indefinite pains" in eight cases. Nausea affected 35 per cent and, contrary to the experience of Pickles, vomiting affected 31 per cent of patients. Abdominal pain was usually generalized or in the upper part; it was in the right lower quadrant in only 10 per cent of cases. Bacteriologic studies were made in 26 cases (Cooper and Keller). Cultures from blood were negative in 23 cases, from spinal fluid in three. Consistently present in nasopharyngeal cultures were green-producing, slightly hemolytic, streptococci. Injected into animals they commonly produced pulmonary lesions, but no definite evidence was obtained that they were the cause of epidemic myalgia.

In true epidemic myalgia, muscles of the chest and abdomen are affected. In an epidemic of some sort of myalgia at Rugby School, England, Smith [633] noted common involvement of neck muscles, which were very painful and tender, often associated with slight fever and regional adenopathy. In "ordinary stiff neck" the neck is turned toward the affected side; in this type the neck was turned away from the affected side, presumably because diseased muscles were so weak their tone was lost.

Myositis Ossificans. Chaudhuri reported a case of progressive myositis ossificans. The patient was a boy two years old. Symptoms were stiff neck and bony protuberances of one year's duration in cervical, scapular, lumbar and sacral regions. Microdactylia was present. Roentgenograms disclosed bony deposits in various muscles. A case of localized post-traumatic myositis ossificans, producing a firm, bony mass on the lateral aspect of a boy's thigh was noted by Hunt. Some consider "rider's bone" an example of traumatic myositis ossificans. Moore reported a case in which a stalactite-like tumor at the origin of the rectus femoris was presumably initiated by riding strains. The etiology of ectopic bone was briefly discussed.

Relapsing, Febrile, Nodular, Nonsuppurative Panniculitis: Weber (1925)–Christian's (1928) Disease. This "new" disease is characterized by crops of subcutaneous nodules which occur during febrile periods and which on histopathologic examination are found associated with a peculiar type of fat atrophy. Eight cases have been reported in the literature; to them Bailey's five cases may be added. Symptoms were recurrent attacks of malaise and fever of widely varying degree, accompanied by subcutaneous nodules; predominant incidence was among women; nodules were on the trunk or extremities, mainly on the thighs; there was a tendency to subcutaneous atrophy with its resultant depression at the site of involution. Pathologic reactions were detailed. The disease may represent a special reticulo-endothelial response in which drugs, particularly iodine, may be precipitating factors. It may cause death.

Diseases of Bursae

It is said that, with the possible exception of subacromial bursae, human beings are not born with bursae; they develop after birth in response to the functional demands of movement (Black, 1934). Superficial bursae (e.g., olecranon, prepatellar, that over the head of the metatarsophalangeal joints of great toes) lie in connective tissue between skin and bony prominences. Deep bursae (e.g., subacromial or subdeltoid and those over the greater trochanter of the femur or over the ischial tuberosity) lie between muscles and moving bony points. The common conditions affecting each were discussed by Kaplan and Ferguson. Chief factors are trauma and infection. [Noninfectious inflammation, as in gout, should be added.—Ed.] As a result of trauma a bursa, previously only a potential space, may fill with serosanguineous fluid and become a palpable, fluctuant sac. With healing, fluid is resorbed but varying amounts of cellular débris and fibrin remain to undergo complete or partial organization. The deep bursae which may be affected are the subacromial (most common), subgluteal, iliopsoas, supratrochanteric, semimembranosus, pretibial. Because of its frequency and special features, subacromial bursitis will be discussed separately.

For acute traumatic bursitis treatment outlined was as follows: immobilization in splints three to four days, by elastic compress bandages longer; cold applications at first, warm ones later; analgesics; aspiration if exudate is marked. For chronic traumatic bursitis the following were recommended: protection from occupational trauma; aspiration and obliteration of sac by sclerosing solutions (details given), or surgical removal if the foregoing fails; heat and aspiration alone are of little value. For suppurative bursitis conservative therapy was advised (splint, hot dressings); later, if the process becomes localized and less acute, incision and drainage. [One of us, J. A. K., advises early drainage.—Ed.]

Wolf discussed bursitis affecting the four bursae of the foot: 1. Those at the dorsum of toes become affected by cramping shoes and pressure of the shoe cap on toes flexed in a claw position. Treatment consists of raising flattened metatarsal arches by foot plates, pads, bandages or rarely by operation. 2. The bursitis at the inner aspect of the bunion joint is usually associated with hallux valgus, less often with osteophytes (hypertrophic arthritis); it is treated by shoe correction, felt or rubber rings and ichthyol ointment. 3. Calcaneal bursitis (without calcaneal spurs) is treated by alcohol dressings, baking, foot support. 4. Achillobursitis is commonly gonorrheal; specific measures or surgical removal were advised.

Moshcowitz noted 20 cases of sartorius bursitis, " an undescribed malady simulating chronic arthritis," affecting obese women, producing pain in both knees, especially on stairs, and resulting from strain of weight bearing. Roentgenograms were negative. Tenderness and occasionally slight swelling were present on the inner aspect of the tibia at the site of the insertion of the conjoined tendon of sartorius, semitendinosus and gracilis tendons. Weight reduction is necessary.

[No surgical proof was given that bursitis, and not tendinitis, arthritis or fibrositis, was present.—Ed.]

Lesions About the Shoulder Joint (Subacromial Bursa and Supraspinatus Tendon). The majority of painful shoulders were once considered due to subacromial (subdeltoid) bursitis. The calcification frequently seen about the shoulder was thought to be practically always in this bursa. Some stated later that the calcification rarely was in the bursa, practically always in the supraspinatus tendon. It is becoming more evident that inflammatory lesions with or without deposits of calcium, and deposits of calcium with or without inflammation, may involve any one (or more) of several different periarticular sites. However, because it is at times impossible to differentiate one affection from the other without anatomic dissection, writers continue to use the term "subacromial bursitis" loosely as a sort of collective term for all these lesions; others use the term peri-arthritis or "para-arthritis" of the shoulder to include lesions due variously to true subacromial bursitis, to major or minor ruptures (with or without calcium deposits) of supraspinatus or other tendons at or near the shoulder, to inflammation with calcification but without rupture of these various tendons, and even to calcium deposits about painless shoulders. Greater accuracy in localizing these deposits can be obtained by making roentgenograms with the humerus in extreme internal rotation. By this means islands of calcium which appeared to be in the head of the humerus were shown by Fahey and Harmon to be actually in tendons of the supraspinatus, infraspinatus or teres minor. Deposits in similar locations were noted by De Lorimier.

Five common causes of painful shoulder were described by Ferguson, and Kaplan and Ferguson:

1. Acute traumatic bursitis from direct or indirect trauma: a traumatic inflammation due to contusion of the bursa between the greater tuberosity and acromion, and to slight tears of the supraspinatus tendon. Symptoms include tenderness over the greater tuberosity, and pain on motion, especially abduction. Roentgenograms are negative. Treatment includes immobilization (adhesive strapping or abduction splint), heat, increasing exercises. Recovery is rapid. 2. Acute bursitis with calcification. Patients so affected have intense, constant pain in the shoulder due to inflammatory tension in regions of calcification. There is acute tenderness over the greater tuberosity and motion is impossible because of pain. Roentgenograms reveal large areas of calcification over the lateral edge of the greater tuberosity. Under local anesthesia, tension in the region of calcification should be relieved by incision and evacuation or by aspiration of the deposits; rapid relief of pain and normal function result. 3. Subacute bursitis with calcification. This is a less severe form of the second syndrome. The shoulder can be moved; it is most painful on abduction or when the patient lies on it at night. Symptoms are due to trauma, calcification and reflex spasm of the supraspinatus. Small areas of calcification appear above the greater tuberosity. It is treated by rest, heat, sedatives, injections of 20 to 30 c.c. of 1 per cent procaine into the bursa, exercises; gradual recovery follows. 4. Chronic bursitis causes pain and "clicking" somewhere during abduction; slight stiffness; tenderness over the greater tuberosity. There are defects in the supraspinatus tendon, villi and bands in the bursa, and excrescences, eburnation, and areas of rarefaction in and at the greater tuberosity. Recommended were rest, heat, excision

of villi, bands and excrescences. 5. Tendinitis or obliterative bursitis results from overuse or repeated slight trauma. Adhesive bursitis causes loss of gliding function in the bursa. Abduction and external rotation become difficult. Atrophy and spasm of shoulder muscles may result. Roentgenograms are negative. Recommended were injections of procaine, manipulation, special exercises, physical therapy. Recovery is slow and may be incomplete.

It was admitted that differentiation into such groupings, especially the distinction between simple bursitis and partial tears of the supraspinatus tendon may at times be difficult to make; however, treatment for the two syndromes is essentially similar.

Patterson and Darrach treated 63 patients with "subdeltoid bursitis" by the double needle irrigation technic of Smith-Peterson. Results in the cases were: complete relief in 57, limited motion in two, operation necessary after irrigation in two, no relief in two. In 48 cases the process was acute (under one week); disability after treatment averaged only five days; in eight subacute cases disability after treatment averaged seven days; in seven chronic cases (more than one month) disability after treatment averaged 10 to 14 days, sometimes longer. Deposits of paste-like calcium were sufficient to show in roentgenograms in 48 cases, but results often were good, even when opacities were not seen; hence, irrigation should not be refused those on examination of whom deposits are not found. The assumption that the deposits frequently were in bursae as well as in supraspinatus tendons seemed correct because paste-like calcium was aspirated in the salt solution. In cases wherein deposits were not in bursae but in tendons, relief often was noted even though deposits remained; at other times irrigations were ineffective.

Irrigation seemed indicated in cases in which initial attacks of very acute pain were localized to one spot, not radiating, and in which fuzzy (not dense, round or bonelike) calcium deposits appear to be in bursa, not in tendons. Other patients were treated by physical measures, perhaps aspiration was tried in resistant conditions prior to surgical exploration.

[It is at times difficult to be sure deposits are in bursae; in obliterating bursitis it is difficult or impossible to thrust even one needle into a bursa.—Ed.]

Clayton accepted the view that in subacromial bursitis the lesion is not in the bursa but in, on or under the supraspinatus tendon, and consists of inflammation, necrosis of the tendon, calcium deposits or metamorphosed fat. He did not accept Codman's (1934) view that deposits are due to acute traumatic rupture of some fibers of the supraspinatus tendon. To him the cause was not trauma, hemorrhage or infection but some undefined metabolic disturbance. In severe cases the most pain may not be at the bursa or the site of the deposit but near the insertion of the deltoid; symptoms may be those of brachial neuralgia. Deformities arise not from adhesions, as some believe, but from contractures of muscles and liganents. In "bursitis" tenderness is limited to a definite area "smaller than a twenty-five cent piece" at the front of the humerus just below the acromion at the

site of the deposit; in chronic arthritis there is tenderness of the entire circumference of the head of the humerus.

Codman is generally recognized as the first to describe rupture of the supraspinatus tendon as a major cause of disability of the shoulders. He has currently written: "As for my own impression that I was the first to call attention to ruptures of the supraspinatus and of the other short rotators, —it has been gently but firmly and permanently removed" by the discovery of a report on the same subject published by Smith, 1834, and reprinted by Codman.

Few surgeons have the opportunity to study the pathology of, and repair ruptures in, supraspinatus tendons within 38 to 72 hours after rupture; Mayer had four such cases, Davis and Sullivan three. Mayer advised certain "important changes" in the technic of surgical repair. Davis and Sullivan also recommended early repair of tendons. Signs necessary for a diagnosis of complete rupture were given and included a history of acute trauma, immediate sharp pain, "a tender point, a sulcus and an eminence at the insertion of the supraspinatus which causes a jog, a wince and soft crepitus as the tuberosity disappears under the acromion when the arm is elevated, and usually also, as it reappears during descent of the arm."

The common disabilities of shoulders are not due simply to acute traumatic rupture of the supraspinatus tendon, according to Skinner, but involve a more widespread disturbance than mere rupture; this is often only an accident in the course of a progressive disturbance involving various structures, but centering around the supraspinatus tendon. Separation of this tendon (which is beneath the floor of the subacromial bursa) from its attachment to the humeral tuberosity has been held to be due to: (1) trauma (rupture and imperfect repair), (2) defects left by calcium deposits, (3) necrosis of tendon or other diffuse pathologic processes, (4) attrition (wear and tear of age). Varied opinions on the mechanism of the deposition of calcium were reviewed. Skinner traced this sequence of events: The anatomic location and function of the supraspinatus muscle are such that it is subjected to stresses which may produce profound changes in the muscle; first is an alteration in the character of its lateral position—from fleshy fibers ending in a short tendon to a wide aponeurosis of fibrous tissue which blends with the infraspinatus. In the muscle weakened thereby other changes ensue: calcification, splitting or rupture of tendon, separation of the sheet from the greater tuberosity, and the establishment of free communication between subacromial bursa and joint cavity. Changes likewise affect the greater tuberosity, intertubercular sulcus and tendon of the long head of the biceps; also, changes take place within the joint. The long head of the biceps is flattened and frayed; the capsular portion of the tendon may disappear. Important factors in the long process of wear on the supraspinatus tendon are the patient's age and occupation. In about 20 per cent of all adult shoulders there are changes in this tendon; in 5 per cent some degree of rupture or splitting will occur.

Among patients benefited by roentgenotherapy, Kahlmeter listed some troubled by acute subdeltoid or subacromial bursitis, "peritendonitis calcarea" and "humeroscapular periarthritis." For these and other bursae "x-ray therapy is very good." The results of De Lorimier were noted. Results of short wave diathermy given in 99 cases of "subdeltoid bursitis" with calcification, resistant to other measures, were good, according to Feldman; pain was relieved by three to six treatments; function was restored after 10 to 12 treatments. Such therapy presumably produced deep heat, marked hyperemia, muscle relaxation, drainage of exudate, reduction of tension on bursal walls. Calcification may not disappear but its failure to disappear bears no relation to end results. Purulent bursitis is a contraindication to such therapy. Similar therapy was advocated by Humphris.

Miscellaneous Conditions

Bone Abscesses Simulating Arthritis. Three patients with articular pain of five to 14 years' duration, treated as arthritis but due to Brodie's abscesses, were noted by Wagner. Such abscesses begin early in life as epiphysitis, often from avirulent staphylococci. They are chronic, never acute and progress for years, producing bone necrosis, areas of rarefaction and of formation of new bone, partial loss of articular function, occasionally synovitis. Pain is "boring" and is referred to a joint and center of affected bone. Roentgenograms of bones in various positions may be necessary for diagnosis. Surgical treatment gives spectacular relief.

Lupus Pernio (Boeck's Sarcoid; Osteitis Tuberculosa Multiplex Cystoides). Features of this disease were excellently reviewed by Longcope and Pierson. This chronic infectious granulomatous condition slowly progresses to involve chiefly skin (eruption, disseminated nodules, large cutaneous nodosities, infiltrations), lymph nodes, lungs ("marbled" or reticulated appearance, diffuse fibrosis) and bones of hands and feet, sometimes other tissues. Fingers may be deformed by subcutaneous nodules symmetrically disposed about interphalangeal joints. In advanced cases there may be relatively painless mutilation, with gradual disappearance of terminal phalanges. Roentgenograms are characteristic: areas of rarefaction and reticulation in medulla of phalanges, sometimes irregular enlargement and distortion of bones but no involvement of periosteum or of joints. Areas of rarefaction often occur as sharply defined, round, punched out spots [and are sometimes mistaken for those of gout, atrophic arthritis or hypertrophic arthritis.—Ed.] Eight new cases were reported; bones were involved in three. The cause is unknown; many consider it a peculiar form of tuberculosis. Data for and against this idea were reviewed.

Other Studies

Experimental Arthritis. 1. Infectious. Rosenow's strains of arthrotropic streptococci were given intravenously to rabbits by Jarløv and Brinch.

Articular lesions were consistently produced; lesions in other organs occurred much less often; thus Rosenow's theory of elective localization seemed to be supported. The severity of articular lesions varied from pyoarthritis to slowly progressive, symmetrical, chronic, deforming arthritis; in some cases hypertrophic lipping of vertebral bodies occurred. Only by motion picture records and close clinical observations were some of the milder articular lesions noted objectively; they were verified by pathologic studies. Such lesions might well have escaped detection in the work of others.

Joint tissues can be damaged by contact with bacterial toxins alone, not necessarily by whole bacteria. Rigdon made single injections of staphylococcus toxin into knees of rabbits. Reactions included periarticular swelling; exudate of erythrocytes, polymorphonuclear and mononuclear cells; fibrinous synovitis; proliferation of fibrous tissue; focal destruction of cartilage; capsular fibrosis; lesions in adjacent muscles.

2. Traumatic. The articular changes produced in animals by acute trauma (Miltner, Hu, and Fang), and those resulting from the chronic trauma from patellar displacement (Bennett and Bauer), already have been discussed (under "traumatic arthritis" and "hypertrophic arthritis" respectively).

3. Chemical. The changes produced by intra-articular injections into animals of indole, skatole and indole proprionic acid (Forbes and Neale) were noted (under "atrophic arthritis—factor of altered metabolism").

Articular Roentgenography. In studying roentgenograms of joints too much attention is paid to bone changes, too little to soft tissues inside and around joints. Roentgenograms made with knees flexed at 125° or at 105° give better views of intercondylar fossae and may reveal hypertrophic arthritis not visible in ordinary roentgenograms. In Jordan's technic, patients lie on their backs; anteroposterior views are taken of knees flexed at 125° and held in this position by a triangular support under the popliteal space. Holmblad found views made by such a technic superior to ordinary roentgenograms but inferior to those taken postero-anteriorly, with patients kneeling with the abdomen supported in a horizontal position, and with the knees flexed at 75° (i.e. at 105° extension). To study the part played by cortex and cancellous bone in the production of roentgenographic images Lachmann made experimental roentgenographic analyses of bones of cadavers. In arthrograms Hosford demonstrated the complete reëstablishment of the synovial cavity of a knee after synovectomy.

Articular Physiology. The full report of Bywater's studies on the metabolism of joint tissues appeared; a short summary of it was given in last year's Review.[4] Kling summarized the studies of himself and others on articular physiology. Morphologic and physicochemical studies and experiments show a dual structure and function of synovial tissues. One part is a connective tissue capsule for the binding of articulating bones. Interposed at the intra-articular surfaces are areas for the elaboration of

synovial fluid. The function of normal synovial fluid is lubrication and protection of joint surfaces. Motion is the physiologic stimulus for the production of normal synovial fluid. The function of synovial fluid depends on its mucin content. Mucin is a product of special cell activity and not of degeneration.

Articular Function. In an effort to establish norms for a comprehensive investigation of the development of human motor function, Glanville and Kreezer determined the range and velocity of articular motion in normal male human adults. The use of a standard method of grading articular disability in cases of arthritis was proposed by Taylor who set up a table of grades of articular involvement as determined by roentgenographic changes and clinical findings.

[One of us (P. S. H.) long has found it useful to summarize each case thus: for example, " chronic atrophic arthritis, activity grade 2, extension grade 3." This gives a concise picture of a patient with moderately active disease affecting many, but not most, of his joints. The use of some such grading as Taylor's, especially by those who report results of treatment, would be of great value in assisting readers to judge for themselves the worth of any procedure. It is one thing to say, for example, that gold cured such and such a percentage of 100 patients with atrophic arthritis: 50 may have had a mild form of the disease, 30 a moderately severe form and only 20 a severe form. The word " mild " is inadequate, as one patient may have mildly active disease in one or two joints, another may also have the disease mildly active but in a dozen joints.—Ed.]

Auscultation of Joints. A survey of the value of auscultation of joints was made by Steindler. In a study of 1600 joints of persons of different ages, Walters (1929) noted grating in only 1.5 per cent of children in the first decade; in 82 per cent of persons in the eighth decade of life. Steindler utilizes a cardiophone and an oscillograph. Sounds emanating from four quadrants of knee joints were studied. Isolated sounds are cracks, clicks or thuds. High pitched cracks indicate hard, dense bodies (e.g. joint mice); low pitched clicks and still lower pitched thuds indicate bodies of greater softness and elasticity (e.g. fringes, semilunar cartilages). Sounds could be localized both as to quadrants and as to position of the joint. Such studies helped to localize loose bodies and injuries to semilunar cartilages. Studies were made on 216 arthritic patients. Results were analyzed in detail.

Physiology of Muscles. Lack of knowledge of the chemical changes which take place in muscles and joints and which cause or result from disease is " colossal." The pathogenesis of many of these diseases will not be fully understood without more information thereon. A number of interesting studies on the physiology of muscles under various conditions were reported but can only be referred to here.[37, 59, 154, 214, 216, 300, 307, 436, 592, 610, 635]

Studies of Pathology. De Galantha described a method for rapid decalcification of bone by which bone can be prepared for sectioning in as little as three to four days. The method also has the advantage of being

less deleterious to cellular elements of soft parts; hence, better cellular and tissue differentiation with elective staining reaction is possible.

The Campaign against Rheumatism

A few generations ago the hot, swollen, beefy-red joints of gouty patients were so effectively dramatized that it became a matter of distinction to boast of a few such joints on one's person or on one's family tree. Times have changed; gout, though still plentiful, is no longer fashionable; nowadays some students of the disease are finding it difficult even to publicize gout, to dramatize its presence for the sake of its better recognition and its earlier and more effective treatment. If this be so, how much more difficult is it to dramatize the cold, clammy, bluish-white joint of atrophic arthritis, particularly when its possessor is often stagnating in his cripple's room at home or perhaps hidden away in some "chronic hospital" as its none too welcome guest. But if the medical profession is to make notable progress in the scientific and sociologic study of this and other rheumatic diseases, there must be some dramatization of such joints, that more money can be obtained from philanthropists for researches on etiology and treatment, that more money will be assigned by hospital boards to increase the facilities of general and special hospitals for the care of the army of arthritics *before* they are "admissible" to the orthopedic wards as cripples, that funds may be set aside for the long-term treatment of arthritics (some as in-patients, most as out-patients) in stages when the most can be accomplished. Truly one atrophic joint is not of dramatic appeal but millions of them together should be. There are approximately 2,000,000 to 3,000,000 American patients with atrophic arthritis and probably each will possess (before his disease stops) an average of four big and six small, affected joints, making a grand total of 20,000,000 to 30,000,000 aching joints in this group alone, thousands of them on their way to ankylosis.

To be fully successful a campaign against rheumatism needs occasional dramatization. But for the ultimate success of such a campaign a sustained, undramatic, slowly progressing growth of interest in the rheumatic diseases among physicians and laymen is much more important than isolated, sporadic days of high resolve. It is along these lines that the campaigns in this country and abroad are being waged. In the United States, the American Rheumatism Association and the American Committee for the Control of Rheumatism have the important and most cordial support of the American Medical Association, which has opened its programs to an increasing number of reports on the problem of rheumatism. "Hygeia" annually publishes a few papers of special interest to arthritic laymen.[178, 389] The American Rheumatism Association has created associate memberships for interested laymen, social workers, insurance executives, members of professions allied to medicine; to them are being sent bulletins summarizing information of current interest. The Association's Conferences on Rheu-

matic Diseases, held annually at the time of the meetings of the American Medical Association, are increasingly well attended. New Clinical Clubs and small groups of physicians meet, in many of the larger cities, for the purpose of special study of these diseases. New research grants have been made for the establishment of "arthritis units" in several university and city hospitals (e.g. at Harvard University, the University of Michigan, and at Welfare Island, New York City).

In the Commonwealth of Massachusetts, which is perhaps the most progressive in the matter of social legislation, as far as the problem of rheumatism is concerned, an act was recently passed providing for the hospitalization of a certain number of patients, and their treatment for periods as long as six months.

The progress and importance of the campaign in England have been reported by Lord Horder and Sir Frank Fox. The Empire Rheumatism Council purposes to instigate research; to endow chairs or readerships at certain university medical schools for conduct of such research; to enlarge the facilities of special and general hospitals and of hydrologic and radiologic institutions for the treatment of rheumatic diseases and to coöperate with such work in foreign countries; to communicate by lectures and by publications knowledge gained as to the cause of rheumatic diseases and the methods for their prevention, alleviation and cure. Medical science has notably increased the span of a man's life but there is danger that too great a fraction of that lengthened span may be spoiled by the painful symptoms of degenerative arthritis, if not by some more serious articular disability. It is now truly Medicine's duty, having added to the quantity of human life, to add also to its quality. Whatever successes are gained by such campaigns against rheumatism will go a long way toward fulfilling that obligation.

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The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1938–1939) articles which will greatly facilitate the preparation of subsequent reviews.

CASE REPORTS

TULAREMIA; A PATHOLOGIC STUDY OF THE LESIONS IN A CASE TREATED WITH SPECIFIC ANTISERUM, THE PATIENT DYING SUDDENLY FROM INTERCURRENT CORONARY OCCLUSION*

By KARL V. KITZMILLER, M.D., F.A.C.P., *Cincinnati, Ohio*

THE increasing prevalence in the use of *Pasteurella tularensis* antiserum, which recently has become commercially available, in the treatment of tularemia, makes the report of a fatal case in which the antiserum was used of special interest at this time. Particularly so, when the fatality is sudden and unexpected, following the antiserum treatment by only a few days. Foshay has stated that in his experience in the specific treatment of these cases he knows of none, with the exception of the advanced, overwhelming infections, in which some associated lesion usually involving the circulatory system has not been responsible for the patient's death. The case herewith reported substantiates this statement. It also offers the first opportunity of observing post mortem the extent and character of the lesions of this disease following antiserum therapy and of comparing them with those of other recorded fatal cases in order to determine, if possible, the effect on healing of the so-called latent lesions, and the relationship of these lesions to the development of immunity to the disease.

The following is a resumé of the history, clinical course† and necropsy record.

CASE REPORT

The patient, E. R., a white male, mechanic, 36 years of age, was admitted to the Deaconess Hospital, December 19, 1934, complaining of "rabbit fever." He stated that on Tuesday, November 27, he went hunting, killed four rabbits, and that night helped his wife to clean them. Saturday afternoon, four days later (December 1) he complained of feeling achey and weak, and that night had two chills followed by profuse perspiration. He remained in bed until Tuesday, December 4, when he felt well enough to return to work. However, at that time he did not feel so well as usual and had frequent night sweats. About December 12, he noticed some soreness and slight swelling about the outer nail bed of the left thumb, which were present on his admission to the hospital. There was no axillary swelling or soreness nor were there other noteworthy complaints. He had lost 10 lbs. since the onset of his illness, four weeks before (November 27, 1934). There was no history of past serious illness.

Physical examination revealed a very well developed, well nourished man, cheerful, coöperative, not appearing acutely ill, with normal pulse, temperature (97.6° F.) and respirations. There were no physical findings of note recorded except the blood pressure, which was 150 mm. of Hg systolic and 100 diastolic, and a small area of induration and tenderness at the base of the left thumb nail. The following

* Received for publication February 12, 1938.
From the Pathologic Laboratory, Deaconess Hospital, Cincinnati, Ohio.
† I am indebted to Dr. Harry Box for permission to record these findings.

laboratory findings were noted: Urine negative, except for a trace of sugar in a single specimen; red blood count, 5,520,000, hemoglobin 85 per cent (Dare), white blood count (12–20–34) 9,300; polynuclear neutrophiles 28.5 per cent (stab forms 18 per cent, segmenters 10.5 per cent); lymphocytes 61.5 per cent; monocytes 2 per cent; eosinophiles 7 per cent; basophiles 1 per cent. On December 22 the white blood cell count was 8,850; polynuclear neutrophiles 50 per cent (stab forms 18 per cent, segmenters 34 per cent); lymphocytes 45.5 per cent; eosinophiles 4 per cent; myelocytes 0.5 per cent. An intradermal test with *Pasteurella tularensis* antigen was positive, December 20.

Agglutination tests were positive (1–640) with *Pasteurella tularensis* antigen on December 21, and again on December 23.

Friday, December 21, two days following admission, the patient was given 15 c.c. of antitularensis serum intravenously with no obvious reaction. The following day 15 c.c. of antiserum were given again with no untoward result. The patient felt very well during his entire hospital stay of five days, his temperature never rising above 100° F. He was permitted to go home December 24, with instructions to return for intradermal testing at weekly intervals. Accordingly, he came to the hospital December 27, 1934, for this test, and at the time remarked that he felt very well and was rapidly gaining his former strength. At six o'clock the following evening, his physician received an emergency call from the patient's wife stating that he had suddenly been seized with cramping pain in the chest and could scarcely breathe. When seen by his doctor he complained of agonizing chest pain, showed evidence of some circulatory collapse. When he had been relieved somewhat by a hypodermic injection of adrenalin, he was immediately taken to the hospital, being admitted at 8:45 p.m. on a stretcher. He had a convulsion shortly after being placed in bed, failed to respond to emergency medication, and died at 8:55 p.m. twenty-eight days after the onset of the disease.

The essential parts of the necropsy protocol follow:

The body was that of a well developed, very well nourished white man, partially bald, with composed features and waxy, sallow facial pallor, apparently about 35 years of age. The skin was pale and elastic with very faint tiny purpuric spots (2 to 3 mm.) over the ankles and insteps. There was some discoloration of the left thumb without swelling, while a clean, dry, linear fissure was present near the base of the nail. The left epitrochlear node was not palpable. The left axillary nodes were discretely enlarged, rather soft and movable, the largest node of this group measuring 3 by 2 by 1 cm. The posterior cervical nodes on the left, and the anterior cervical nodes on the right measured approximately 1 cm. in diameter. There was also a small (1 cm.) palpable node in the right axillary space. The right epitrochlear and the inguinal nodes were not palpable.

The peritoneal cavity possessed a smooth, glistening lining, and contained no free fluid. Numerous fine feathery adhesions extended from the spleen to the inferior surface of the left lobe of the liver. The stomach was of average size, normal contour, and contained a small amount of partially digested food. There was slight uniform edema and softening of the intact, grayish mucosa, with widely spread, fine petechial extravasations, and engorgement of the tiny mucosal and submucosal vessels. The duodenum, of normal size, had a dark, grayish red, softened, edematous lining. There was some softening of the mucosa of the large and small bowel with normal appearing lymphoid structures. The appendix was small and retrocecal, showing no evidence of recent or past inflammation. A group of discretely enlarged, soft, white lymph nodes (1 to 1½ cm.) was found about the common bile duct, duodenum and head of the pancreas. Section showed the majority of these to be completely liquefied, containing milky, puriform fluid.

Cultures taken on blood cystine dextrose agar by Dr. Lee Foshay failed to grow *Pasteurella tularensis.*

The liver weighed 2280 grams, possessed full rounded contours and glistening, thin capsule. The brown and grayish yellow external surfaces were diffusely mottled with grayish patches and streaks. Occurring every 5 to 10 cm. were white, miliary subcapsular foci, measuring 1 to 2 mm. in their greatest extent, surrounded by dark, purplish hyperemic halos 3 to 4 mm. in diameter. Similar miliary lesions, occurring less frequently, were seen on section of the parenchyma. The cut surfaces were everywhere edematous, tawny, softened, granular, and greasy with the normal markings completely obscured. The spleen was enlarged, weighing 330 grams. The capsule was not greatly thickened, but was roughened, granular and of grayish slate color. Section revealed bright, reddish gray, adenoid pulp, with hyperplastic follicles and obscured trabecular markings. Scattered throughout the organ were small focal areas of softening, with a few soft, white, cheesy, necrotic lesions (4 to 8 mm.).

The kidneys together weighed 330 grams, with pale, gray, thin, glistening, tense, readily stripping capsules, and congested subcapsular vessels. The external surfaces were smooth and marked with pressure indentations. On section, the cut surfaces possessed a yellowish, gray, mottled appearance, while the cortex was broad and granular and the striae obscured. The grayish, glistening pyramids had dark red, passively congested borders. The linings of the pelves and ureters were soft and pallid. The bladder was contracted, possessing a pale gray slate-colored, slightly edematous mucosa. It contained a few cubic centimeters of cloudy, straw-colored urine.

The pleural cavities contained no free fluid and possessed smooth, glistening linings, while the grayish white, fully crepitant lungs presented an entirely normal appearance. The peribronchial lymph nodes were small and compact, and the branches of the bronchial tree and pulmonary vessels were not remarkable.

The lining of the pericardial cavity was smooth and glistening, and the small amount of fluid clear and straw-colored. The heart was of average size, weighing 280 grams. The dark, purplish atria bulged prominently, and the left ventricle was flabby and bulbous. There was a small amount of epicardial fat, and an irregularity of the left ventricular wall, as noted on palpation; also a small, thin, tough, fibrinous area in the anterior wall of the right ventricle. The chambers contained dark fluid and recently clotted blood. Advanced subendocardial myomalacia was noted in the right and left ventricular walls, involving portions of many of the papillary muscles. The valvular leaflets and cusps were soft and delicate, while the valvular orifices were of normal size. The heart measurements follow: T.V. 120; M.V. 90; P.V. 75; A.V. 70; T.L.V. 16; T.R.V. 8; T.L.A. 2; T.R.A. 1. The sectioned myocardium possessed glossy, softened, brownish red cut-surfaces, with coarse muscle-bundle markings, and scattered, yellowish gray, and grayish brown foci. There were also frequent focal and linear fibrous scars, with extensive atheromatous plaquing, and partial occlusion of the small coronary arteries: Partial occlusion of the orifices of the right and left arteries was brought about by the encroachment of white and pale yellowish white, slightly elevated, smooth, oval plaques in the sinuses of Valsalva. The coronary vessels were everywhere semi-rigid, projecting noticeably from the cut-surfaces.

There was some atheromatous streaking of the aortic arch and thoracic aorta, with no characteristic linear striations of the intima. Microscopic examination of the heart muscle showed advanced fibrosis with the muscle fibers arranged in a loose connective-tissue meshwork. Many of the individual fibers were hypertrophied with irregular, pyknotic nuclei and fairly well preserved sarcoplasm, while in many subepicardial areas there was complete fibrosis with relatively acellular, hyalinized connective tissue. There was also widespread scarring where a few small fibers remained in very fibrous, cellular connective tissue. A large, healed infarct was seen in the wall of the left ventricle, and also a very fresh infarct showing hemorrhagic necrosis of most of the affected fibers. Nearby was a sclerotic artery with a

small, irregular, fibrinous thrombus incorporating a few blood cells and several particles of brownish amorphous pigment, attached to one side of the vessel wall but not entirely occluding the lumen. Practically all the coronary arteries showed sclerosis with thickening of the intima, hyalinized connective tissue in the muscularis and adventitia, and areas of fatty degeneration and calcification of the intima and media.

The following information was obtained upon microscopic examination of sections from various other organs.

There was some thickening of the pulmonary alveolar walls with scattered monocytes and numerous pigment-laden phagocytes, slight peribronchial fibrosis, active mesarteritis, but no lesions of the lungs characteristic of tularemia.

The liver showed multiple, large, granulomatous lesions with massive caseous centers, radiating peripheral zones of fibroblasts and fibrous connective tissue, occasional large foreign-body giant cells, scattered mononuclear and lymphocytic infiltration, and an outer zone of fairly dense cellular exudate composed largely of mononuclears, lymphocytes, macrophages, a few scattered polymorphonuclear leukocytes, necrotic liver cells and some bile pigment. Around most of these lesions, in the parenchyma, immediately outside the exudate, there were a number of large vacuoles, not taking fat stains and containing varying amounts of yellowish brown and black amorphous pigment, which when scattered or lying near the borders of the larger masses had a spinous, needle-like appearance. (Figure 1.) The pigment failed to show evidence of hemosiderin or iron, with special staining technic. These collections were interpreted as inspissated bile derivatives in dilated canaliculi, occluded as the result of blockage of the local bile circulation near these larger destructive lesions. (Figure 2.) Many liver cells in these areas also contained finely divided bile pigment in the cytoplasm. There were also scattered miliary granulomatous foci without central necrosis and with no, or very little, fibroblastic proliferation. There was much peripheral fibrosis in some of the larger focal lesions, with monocytic and lymphocytic infiltration of the periportal spaces. The portal and hepatic veins contained unusual amounts of dark brownish amorphous and crystalline pigment. The remaining parenchymal cells had pale, mushy, granular, confluent cytoplasm and pale, swollen, vesicular nuclei with prominently bulging membranes and fragmented chromatin.

Focal tularemic lesions similar to those seen in the liver were found in the spleen. There was also active and passive congestion of the pulp with large numbers of monocytes, and areas of hemorrhage associated with marked pigment deposition and pigment-laden macrophages. The capsule was swollen and in places infiltrated with monocytes. The vessels were sclerotic and there was much intravascular, dark brown, partially phagocytized pigment.

In the mesenteric lymph nodes there were massive granulomatous lesions with large caseous centers, peripheral fibrosis, monocytic and lymphocytic infiltration, and numerous foreign-body giant cells. There was also some edema of the pulp with scattered endothelial infiltration.

Sections from the kidneys revealed advanced degenerative changes in the renal epithelium, the cells being pale, poorly stained and confluent, with many missing nuclei. The lumens of the tubules contained pale, granular material, with hyalin casts in some of the collecting tubules. There was much connective tissue in the cortex surrounding groups of dilated tubules, and excessive fibrosis in the medulla, obstructing and obliterating many of the tubules. The glomeruli were large with hyalinized capsules and somewhat shrunken, hyalin-thickened tufts with few nuclei, scattered dark brownish yellow pigment granules, frequent intracapsular adhesions, and occasional small amounts of granular exudate. The vessel walls showed extensive sclerosis, with much dark, brownish pigment in the epithelium of the collecting tubules.

FIG. 1. Low power microphotograph of focal tularemic lesion in the liver, showing dilatation of adjacent bile canaliculi.

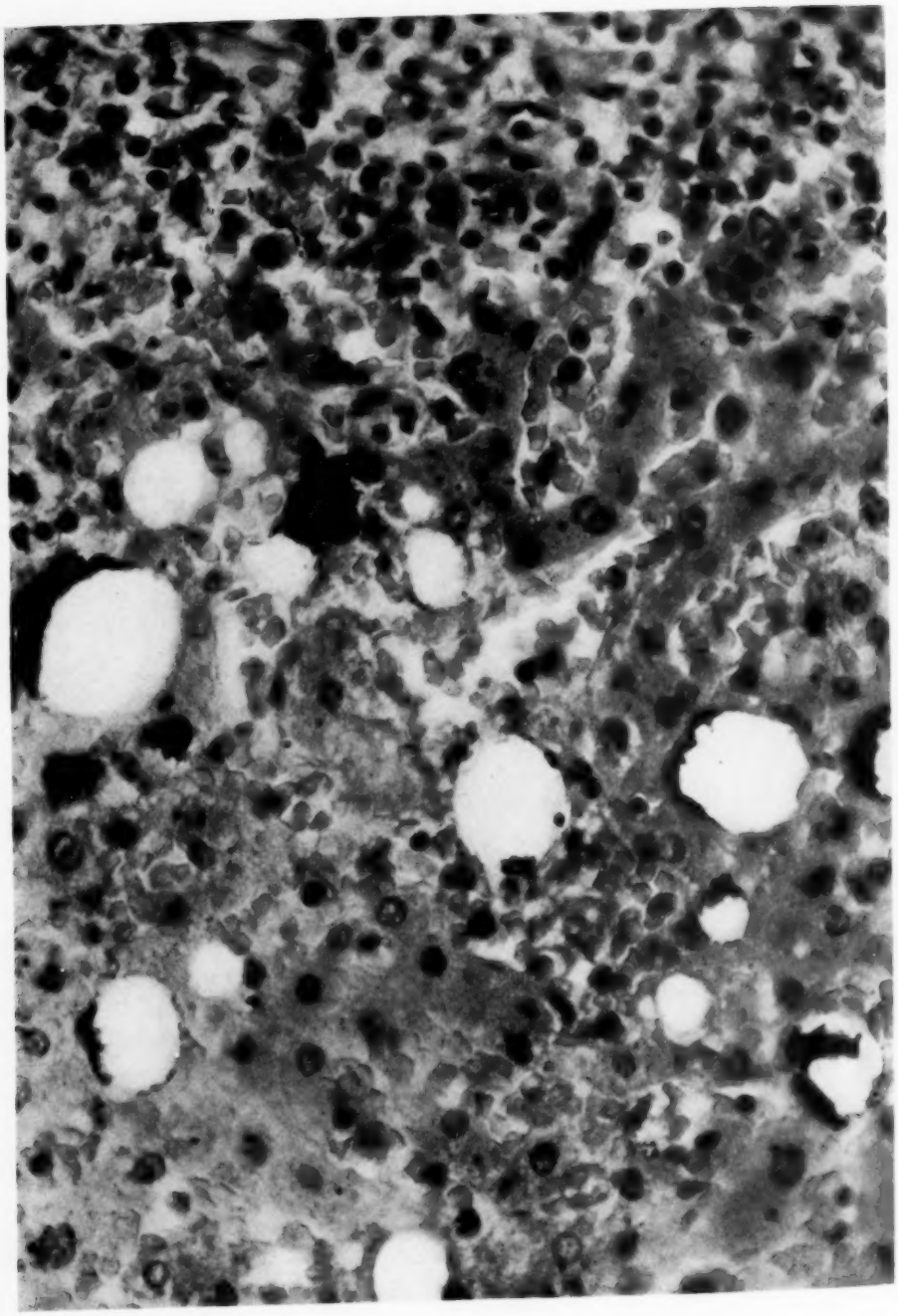

FIG. 2. High power microphotograph of the liver, showing the dilated bile canaliculi containing inspissated bile pigment.

Discussion

The noteworthy feature in this case is the occurrence of a clinically mild tularemic infection in a young man with seemingly good resistance, who dies suddenly several days after the administration of specific antiserum. Necropsy discloses extensive, severe coronary heart disease as responsible for death, and well established focal tularemic lesions throughout many of the organs of the body, the extent and morphologic character of which would lead one ordinarily to expect an active clinical infection. What rôle the antiserum played is difficult if not impossible to estimate, judging from the character of the lesions alone. These are in all respects similar to those found in the subacute clinical disease of the well defined granulomatous type as it occurs in man. Fibroblastic proliferation and chronic inflammatory cellular exudate are well defined but not sufficiently different from the lesions seen in other non-serum-treated cases to be of significance.

Comment has been made in a previous article * on the deleterious influence of tularemia on previously damaged hearts. The damage from this infection is apparently due both to toxemic effects on the myocardium and coronaries and to focal lesions which may result in vascular occlusion.

Of particular interest in the pathology of tularemia are the liver lesions noted in this case, certain details of which to my knowledge have not been previously recorded. Aside from the focal and diffuse toxic changes usually seen there are numbers of scattered discrete lesions of the external and sectioned surfaces first noted on necropsy as white miliary, subcapsular foci, measuring 1 to 2 mm. in their greatest extent, surrounded by dark purplish halos, 3 to 4 mm. in diameter. These halos are disclosed microscopically as composed of groups of dilated bile canaliculi containing bile or bile derivatives, and occluded as the result of blockage of the local bile circulation by the large, destructive, caseous lesions in the parenchyma.

Summary

A case of relatively mild tularemia is presented, the patient dying suddenly of an intercurrent coronary thrombosis shortly following specific antiserum therapy.

Extensive coronary and myocardial disease is disclosed at necropsy as well as the active lesions of tularemia.

Unusual lesions of the liver are discussed.

Nothing in the protocol suggests any untoward effect resulting from the use of the specific antiserum.

* Foshay and Mayer: Viability of *Bacterium tularense* in human tissues, Jr. Am. Med. Assoc., 1936, cvi, 2141.

Fig. 2. High power microphotograph of the liver, showing the dilated bile canaliculi containing inspissated bile pigment.

CASE OF MYATONIA CONGENITA TREATED SUCCESSFULLY WITH ADRENAL CORTEX (ESCHATIN) *

By MAX H. WEINBERG, F.A.C.P., M.D., *Pittsburgh, Pennsylvania*

Myatonia congenita has attracted a great deal of attention, in spite of its comparative rarity, ever since the condition was first described by Oppenheim in 1900. In 1917 Reuben [1] could gather from the literature only 130 cases and reported on six of his own, the highest number reported by one observer. The majority of the reports deal with but one or two cases. Most of the reports are concerned only with description of the disease and the central point of the discussion is, usually, whether it is a separate entity or merely another manifestation of the Werdnig-Hoffman type of infantile muscular atrophy. Very little has been written about treatment. The usual statement is that there is no treatment other than palliative, and that although a certain amount of improvement does set in in some cases, no case is known in which the patient walked again without ataxia or a "waddle" (Kerley and Blanchard,[2] Shuman [3]). Reuben [1] makes the emphatic statement that "The prognosis as to recovery is absolutely bad; there is no record of a complete recovery in a single case." He points out that of infants of one year or less suffering with this disease, whose fate is known, 70 per cent died, and adds: "One cannot understand why it is, in the face of these statistics, that many writers give such a favorable prognosis in this disease."

The rarity of *myatonia congenita,* and the complete recovery of our patient on a specific type of therapy have led the writer to report the following single case in order that the treatment may be tried by other observers, who may have the opportunity to see more patients suffering with the condition.

CASE HISTORY

B. J. S., a female child, aged 20 months, was admitted to the hospital on January 15, 1937, with a history of inability to stand or walk for the past four weeks, sleeplessness, and restlessness for the past three or four months. Around the middle of December 1936, the mother noticed a gradual development of weakness in the lower extremities which progressed to a complete loss of motor function. A gradual weakness of the arms was also observed, but to a lesser degree.

Neurological examination revealed an apparently well developed child; closed fontanelles; rapid pulse; excessive perspiration; normal cranial nerves; practically complete loss of the deep reflexes of the arms, and complete loss of those of the lower extremities; marked hypotonia of all the extremities; flail-like joints of the legs especially—the legs could be brought up easily and the feet placed back of the neck; and complete inability to walk, stand, or even turn over in bed.

A diagnosis of *myatonia congenita* (Oppenheim) was made.

Electrical tests gave the typical reaction of myatonia. Dr. H. Jacox reported as follows: "Electrical muscle testing reveals a most unusual condition. The child is able to withstand the full output of faradism without crying. This dose is larger than the normal adult can stand. However, there is response in both thighs to only the strongest galvanic current over the motor points. We did not get much response to faradism in the thighs, although we did in the legs. The condition is less marked in the upper extremities."

* Received for publication January 26, 1938.
From the Neurological Service of the Western Pennsylvania Hospital.

For a few days the child had a rise in temperature, on two occasions as high as 102° F. The laboratory tests were essentially negative with the exception of a moderate relative lymphocytosis, 43 per cent small, and 11 per cent large lymphocytes.

Because of theoretical considerations, it was decided to use an adrenal cortex extract (Eschatin *) by subcutaneous injection. The child lived a distance from the city, and because of the parents' insistence on taking the child home, it was decided to have the family physician, Dr. D. Gordon Jones, carry out the treatment.

The dosage given was as follows: Three injections of ½ c.c. Eschatin, three times a week for six weeks; two injections weekly for six weeks; and one to two injections weekly for eight weeks.

On March 16, 1937, five weeks after initiation of the treatment, the mother wrote, "She can use arms and fingers real good, and can almost turn in bed. She can take two steps with left foot, but drags right foot. Can also feed herself."

Reëxamination on April 5, 1937 revealed that hypotonia and flail joints were still present, but that the patient could move her legs voluntarily. She cried and resisted so much, however, that her gait could not be tested, although the mother stated that the child could take steps without any support.

Unfortunately, once the child improved, the people refused to coöperate any further. We could not induce them to bring the child to the city for another neurological examination or electrical testing, which we were particularly eager to do.

December 12, 1937. Reëxamination at the patient's home:

Mother states that the child walks to the center of the town, a distance of half a mile, frequently. The last symptom she observed was a difficulty which the child experienced in getting up from the floor, mostly "a stiffness in the hip joints," and that at times it is noticeable even now when the child is tired.

The child is very well developed. She walks normally, and uses her arms well. On having her rise from the floor, no difficulty is discernible. There is no hypotonia. The deep reflexes of the arms are diminished. The patellar reflexes are absent. The Achilles jerks are present and within normal limits.

Discussion

The writer is fully cognizant of the fact that one successful case does not justify making any claims, but on theoretical grounds it seems that this treatment offers something definite in the condition under discussion.

The reasoning that was followed for the use of adrenal cortex was based on the fact that only recently quinine was found by Wolf [4] to be practically a specific for *myotonia congenita* in his first report of four cases. This was corroborated by Smith,[5] and another series of four cases of *myotonia congenita* and *atrophica* was reported by Kennedy and Wolf [6] with good results. I started out from the premise that *myatonia congenita* is the very opposite condition of *myotonia*. This is obvious, of course, primarily by the hypotonia as contrasted with the markedly increased tone in *myotonia*, and secondly, by the electrical reactions. In *myatonia congenita*, the resistance to electrical currents, especially the faradic current, is well known and even considered of great diagnostic importance; whereas in *myotonia congenita*, the resistance to electrical current is much diminished. I, therefore, decided to use adrenal cortex which is known to be an antagonist to quinine.

While there is a definite pathological picture in this condition pointing to changes in the cord and anterior roots, as well as in the muscles, there is a difference of opinion as to the rôle this plays in the disease. It is believed by

* Parke Davis and Co.

some that the neuro-pathologic changes are secondary to the disease in the muscular apparatus, and that the changes in the anterior horn cells, the occasional changes in the twelfth nucleus and motor roots are due to lack of stimulation resulting from the inactive muscles. Reuben [1] states it thus: "To us it appears that the pathogenesis of this disease is to be sought in a primary abiotrophy of the musculature, and a secondary failure of proper development of the whole nervous system (cerebrospinal axis and peripheral nerves) brought about by deficient natural stimulation to its growth by the abiotrophic musculature." Albanese,[7] more recently, in offering an explanation for the improvement in the frequently seen contractures, as a result of orthopedic measures, says: "Most authors seem to agree that the cause of *myatonia congenita* is a hypogenesis of the peripheral spino-muscular neurons—the cause being so far unknown—which acts during embryonal development." He then goes into a discussion of "triple tonic innervation" as advanced by Luisada, and the muscle changes described by Fiore and Guidi, and concludes that changes take place in the terminal plaques of Boeke. As additional proof of the tone disturbance originating peripherally, he adduces the fact that in many cases of *myatonia congenita,* in the presence of marked deficiency of tone, muscular contractility is well preserved. He concludes his argument with the following statement: "In such a manner, we can state that the successive improvement is due partly to peripheral stimuli resulting from the establishment of activity, be it ever so limited, of the muscular function. In this manner, we could bring about the cure in tendons not only in invigorating the nascent functions of muscular tone, but also in reawakening the contractile functions."

One more link in the chain of evidence is the fact, more recently established by Richter and Levine,[8] that following sympathectomy, there is an increase in the electrical resistance of the skin. One of the most characteristic symptoms of *myatonia congenita* is a marked increase in resistance to electrical currents. It is conceivable, then, that there may be in this condition a marked disturbance of the sympathetic system as a whole, including the adrenals. Bing,[9] states that the adrenal has been "denominated directly as the 'accessory apparatus of the sympathetic.'" Howell [10] states: "Langley has called attention to the peculiar fact that the action of adrenal extracts or solution of adrenalin on plain muscles resembles always the effects of stimulating the sympathetic nerves supplying the same tissue." And again (p. 844) "Removal of this secretion—adrenalin—results in a marked loss of muscular tone and vigor, exhibited by the blood vessels, the heart, and the skeletal muscles, and death follows rapidly." Many cases of *myatonia congenita* have developed after an acute infection. Indeed, this case that I am reporting had some sort of an obscure infection as was evidenced by the rise in temperature. It is well known, also, that infections are frequently followed by transient hypadrenemias. Thaddea,[11] as reported in the Year Book of Neurology and Psychiatry 1935, calls attention to the deleterious effect of infection in Addison's disease. The Year Book Editor's comment on this work is as follows: "Thaddea's two papers point out not only the intimate connection between adrenal cortical function and carbohydrate metabolism, but also the way in which infections probably reduce cortical function temporarily."

It is reasonable, then, to postulate that *myatonia congenita* is perhaps due to a poorly developed sympathetic system more defective in certain cases than in

others; that in some it takes an infection to precipitate the condition, whereas in the more severe cases, the condition manifests itself very early in infancy independent of an aggravating infection.

I believe that it is for this reason that Eschatin proved so beneficial in this case. It is because of its potency as a cortical extract that I selected it for trial, and the results in this case, at least, are striking. Whether it will be equally as effective in cases occurring spontaneously without infection remains to be determined. Other endocrine products, including epinephrine had been previously tried but with indifferent results. The writer feels that the results obtained in this case warrant further trial of adrenal cortical extracts.

If the assumption that the condition is primarily the result of a faulty development of the entire sympathetic system bringing about changes in the central nervous system because of lack of stimulation from the musculature is correct, it stands to reason that the earlier the treatment is instituted, the less damage will have taken place, and the better will be the chances of beneficial results.

Conclusions

1. A case of *myatonia congenita* (Oppenheim) is reported, which recovered fully while under treatment with adrenal cortex (Eschatin) over a period of about five months.

2. A theoretical basis for this treatment is advanced, namely:

a. That this condition being clinically the opposite of *myotonia congenita* for which quinine seems to be a specific, should respond to the treatment with the antagonist to quinine, and,

b. That the condition seems to be due to a disturbance of at least certain parts of the sympathetic system.

3. It is hoped that other observers who have an opportunity to see such cases will try this treatment.

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3. Shuman, J. R.: Amyotonia congenita: report of two cases, Arch. Pediat., 1926, xliii, 225–234.
4. Wolf, Alexander: Quinine: an effective form of treatment for myotonia, Arch. Neurol. and Psychiat., 1936, xxxvi, 382–383.
5. Smith, W. A.: Quinine treatment of myotonia congenita, Jr. Am. Med. Assoc., 1937, cviii, 43.
6. Kennedy, Foster, and Wolf, Alexander: Experiments with quinine and prostigmin in treatment of myotonia and myasthenia, Arch. Neurol. and Psychiat., 1937, xxxvii, 68–74.
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8. Richter, Kurt P., and Levine, Maurice: Sympathectomy in man; its effect on the electrical resistance of the skin, Arch. Neurol. and Psychiat., 1937, xxxviii, 756–760.
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EDITORIALS

THE POSTGRADUATE COURSES

Many members of the College are probably debating still the advisability of attending one or another of the postgraduate courses which have been arranged for their benefit in St. Louis, Chicago, Nashville and Baltimore. Each member of the College has received a program which contains most of the important data. A survey of these courses can not but impress one with the opportunity they offer for a concentrated review of certain fields of internal medicine.

One of the outstanding features of the annual Sessions of the College has always been the visits to the various clinics in the city in which the meeting was held. This opportunity to see " work in progress " and to meet the men who were making notable contributions in various fields is a part of the Sessions especially cherished by many of the members. In a sense, the Postgraduate Courses are an extension and an intensification of this same form of educational experience.

Those who decide to attend will have for a period of one or two weeks the experience of forming part of a small group for whose benefit all the resources and all the latest information of one or more of the leading medical schools of the country will be systematically made available. The stimulus of close contact with the working methods of these institutions, and with their outstanding teachers, and the privilege of informal discussion of clinical or scientific subjects will be theirs.

A study of the program reveals that each course varies somewhat from all the others as to the amount of didactic work, the opportunity to study cases, the amount of time devoted to the underlying scientific bases of clinical medicine. Each man may find what he feels that he most requires.

The enthusiastic reception given to last year's courses is the best guarantee that those who attend this year's will likewise feel that to take part in this aspect of the College's work is one of the most valuable privileges of the Fellows and Associates.

SURGICAL THERAPY IN CONGENITAL INTRACRANIAL ANEURYSMS

Intracranial aneurysms due to congenital weakness of the arterial wall occur chiefly at the base of the brain on the vessels forming part of the circle of Willis, or on closely adjacent arterial trunks. There is a marked tendency for such aneurysms to develop at the site of vascular bifurcation or branching. At these sites congenital defects of the elastic and muscular elements of the arterial wall occur. The aneurysms are occasionally multiple in the same individual. They show great variations in size but the majority are small, like a " minute berry growing from a stem." [1] The occurrence of

[1] FORBUS, W. D.: On origin of miliary aneurysms of cerebral arteries, Bull. Johns Hopkins Hosp., 1930, xlvii, 239–284.

this stem between the artery and the main aneurysmal dilatation is a point of importance and the frequency of its occurrence at different stages of development of the aneurysm needs further study.

We are in need also of further data concerning the relative frequency of occurrence of the congenital type of aneurysms on the individual arteries. From the point of view of accessibility and of the possible effects of ligation it is of importance whether an aneurysm arises from the basilar artery, from the internal carotid proximal to the circle of Willis, from the circle of Willis itself, or from such arteries as the middle cerebral, anterior cerebral, etc., at points distal to the circle of Willis. Various compilations from autopsy records are available but they rarely distinguish clearly between the small congenital lesions and the various aneurysmal dilatations due to vascular degeneration in the aged. We do not know clearly what proportion of the total number of congenital aneurysms lie in situations now accessible to direct surgical attack, or where they might be influenced by extra- or intracranial carotid ligation.

Congenital aneurysms may present symptoms before they rupture; or fatal bleeding may be the first clinical event; or there may be repeated attacks of subarachnoid hemorrhage with or without the presence of localizing symptoms between the attacks.

From the point of view of improving the therapeutic outlook the group of cases showing symptoms before rupture is that which deserves the most careful attention. Unfortunately, for the most part such symptoms are seen only in cases in which the aneurysms are of considerable size, but this is by no means always the case. A very small lesion if located in close relation to the course of the cranial nerves may cause localizing symptoms. In most instances of this kind, so far, the clinical diagnosis has been brain tumor rather than aneurysm. Borchardt [2] reported 11 craniotomies by well known neurosurgeons in various countries in which quite unsuspected intracranial aneurysms were discovered. However, in an increasing number of instances the diagnosis of intracranial aneurysm is being suggested because of characteristic localizing signs, prior to the occurrence of the syndrome of subarachnoid hemorrhage. Most of such cases are aneurysms of the internal carotid whose ophthalmoplegic and visual tract effects have been carefully studied (Jefferson [3]). Aneurysms of the internal carotid in the cavernous sinus or just at the point of exit produce oculomotor paralyses (III, IV, VI) and not infrequently severe orbital and head pain (V) on the side of the lesion. Anesthesia in the area of distribution of the ophthalmic division of the fifth nerve is also characteristic. The anatomical relations of the cavernous sinus readily explain such effects. Those aneurysms arising from the internal carotid between its exit from the cavernous sinus and its junction with the circle of Willis are more apt to produce ocular syn-

[2] Borchardt (ref. Schmidt, Hans): Aneurysmen der Hirnarterien, etc., in Krause: Die Spezielle Chirurgie der Gehirnikrankh.

[3] Jefferson, Geoffrey: Compression of the chiasma, optic nerves and optic tracts by intracranial aneurysms, Brain, 1937, lx, Part 4, 444–497.

dromes of chiasmal or prechiasmal type with characteristic field defects. Jefferson calls attention also to the frequency of mental symptoms.

There are also available many instances of vertebral and basilar aneurysms with suggestive localizing signs arising from pressure on the seventh, eighth, ninth and tenth nerves as well as from pressure on the motor tracts and medullary centers. These, however, have usually been arteriosclerotic fusiform aneurysms rather than saccular congenital lesions and hence have little therapeutic interest.

Since congenital intracranial aneurysms are not of exceptionally infrequent occurrence as compared to other space-occupying lesions, their presence should be suspected when localizing symptoms of the above mentioned types are discovered in the clinical examination. Further help in diagnosis may be obtained from observation of spontaneous remissions in the symptoms over considerable periods of time and of exacerbations associated with sudden and severe head pain. Such attacks are not necessarily associated with the full syndrome of subarachnoid hemorrhage.

Rupture of the aneurysm with sudden and rapidly fatal subarachnoid hemorrhage, or hemorrhage into the brain substance, may terminate a period characterized by such localized signs as those above described, or may occur as the first evidence of the presence of an aneurysm.

However, in a considerable percentage of cases the first hemorrhage or leakage is not fatal. A patient in whom spontaneous subarachnoid hemorrhage has been recovered from, therefore presents interesting diagnostic and therapeutic problems. Since rupture of an intracranial aneurysm is by far the commonest cause of spontaneous subarachnoid bleeding it is important to search for the localizing signs which would indicate the site of the leaking aneurysm. From the history, or from observations made in the period preceding the attack a clue may be obtained in some cases. Even more frequently the extravasated blood about the aneurysm will have produced the first evidence of pressure effects. In many instances, however, no such localizing symptoms are discoverable either before or after the attack.

It is evident that since intelligent therapy depends upon localization of the lesion, further data than those furnished by the pressure effects of the aneurysm itself or of the peri-aneurysmal clot are highly desirable.

Sossman and Vogt [4] first called attention to certain roentgenographic appearances which may be helpful in diagnosing aneurysms of the intracranial portion of the internal carotid artery. These depend upon (1) calcification in the wall of the aneurysm which when present may show as thin semilunar shadows, convexity upward, lying alongside the sella and (2) erosions of bone by the aneurysm usually involving one or both clinoids on one side and a part of the sphenoid body on the same side. Others have confirmed the occasional value of these signs.

The development of cerebral arteriography by Egas Moniz [5] has led to a wide use of this method in certain clinics, chiefly foreign, for the study of

[4] Sossman, M. C., and Vogt, E. C.: Aneurysms of the internal carotid artery and the circle of Willis from a roentgenological viewpoint, Am. Jr. Roent. and Rad. Ther., 1926, xv, 122.

[5] Moniz, Egas: Angiographie cérébrale, Paris, 2nd edit., 1934.

cerebral vascular anomalies, aneurysms, vascular tumors and displacements of brain substance by space-occupying growths. The opaque medium now used, thorotrast, is injected into the carotid (common or internal) and immediate roentgenograms of the skull then will show outlines of the anterior group of arteries. In a considerable number of cases the presence and exact site of a congenital sacculated aneurysm has been well demonstrated by this means.[5, 6, 7, 8, 9, 10] Even the important detail of the presence of a pedicle may at times be shown. Aneurysms in surgically accessible areas are those most apt to be well visualized by carotid injection.

The disadvantages of cerebral arteriography are obvious. Some have punctured the carotid artery through the skin but more usually the artery has been exposed,—an operative procedure which, at least for those who prefer injecting the internal carotid, often presents considerable difficulty. The timing of the injection and of the exposure of the film is a highly technical matter. Finally there is an undeterminable factor of risk which comes from the storage of the thorotrast in the body. On the other hand many hundreds of such injections have now been made yielding successful arteriographs and unaccompanied except in a very small per cent of cases by any detectable reaction. As for the late consequences from the alpha ray activity it is still too early to state what these may prove to be. However, since the amount of thorotrast injected is quite small (8–12 c.c.) in comparison with the amount (75 c.c.) used in hepato-lienography and since Yater[11] and others after extensive experience with the latter method over a number of years have not seen late harmful effects it may be said that the risk in cerebral arteriography is minimal as compared to the dangers of intracranial aneurysm.

The surgery of intracranial congenital aneurysms is still, relatively speaking, in its infancy. The methods available are (1) ligation of the internal carotid in the neck on the side of the lesion; (2) supracavernous intracranial ligation of the internal carotid; (3) ligation of branches of the circle of Willis on either side of an aneurysm; (4) clip ligation of the pedicle of a carotid aneurysm.

Ligation of the internal carotid in the neck is currently the most frequently applied procedure. It is evident that its best chance of success is limited to intracranial aneurysms of the carotid trunk below the circle of

[6] Bramwell, E.: Leaking aneurysm as a cause of third nerve paralysis with special reference to two cases in which diagnosis was confirmed by arterial encephalography, Trans. Ophth. Soc. U. Kingdom, 1934, liv, 205.

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[10] Riechert, T.: Kreislaufstörungen im Hirn im Arteriographischen Bild, Ztschr. f. d. gesam. Neur. u. Psych., 1938, clxi, 426–429.

[11] Yater, W. M., Otell, L. S., and Hussey, H. H.: Hepatosplenography with stabilized thorium dioxide sol: a follow-up study of 200 patients examined over a period of five years, Med. Ann. Dist. Col., 1936, v, 241.

Willis. Its danger lies in the possibility that the collateral circulation through the circle of Willis may be insufficient to supply the brain on the side of the ligation, or that ascending thrombosis may result in occlusion in the communicating arteries. Temporary carotid occlusion affords some opportunity for estimating the collateral circulation but can hardly offer dependable assurance of its efficiency. The reality of the danger is shown by a series of fatalities or permanent paralyses which have followed this ligation. Da Costa estimates that 20 to 25 per cent of carotid ligations develop evidence of intracranial damage. On the other hand there have been a number of successes reported in instances of intracranial aneurysm. Only prolonged observation, however, can show how permanent such cures will be. It is evident that the dangers of carotid ligation are less in younger patients. The fact that many congenital aneurysms come to treatment under 40 years of age has a bearing on this point.

The intracranial supracavernous ligation of the trunk of the internal carotid has been employed in conjunction with neck ligation of the same vessel as a means of controlling the traumatic arteriovenous aneurysms in the cavernous sinus. It has not been applied to saccular aneurysms.

In 1936 Norman Dott of Edinburgh localized by arteriography a small aneurysm at the junction of the left anterior cerebral artery and the anterior communicating artery. He was successful in applying silver clips to the anterior cerebral on both sides of the aneurysm. The patient died of a postoperative mishap before the effects could be estimated. W. Tönnis of Berlin refers briefly to an aneurysm of the anterior communicating artery which he localized by arteriography and successfully operated upon in 1935. Recently (1938) Dandy [12] has reported a brilliant success in a case of congenital aneurysm, which was diagnosed clinically and localized by Ford prior to frank rupture, on the basis of sudden severe pain in the right frontal region and right eye followed by rapidly progressive paralysis of the right third cranial nerve. Using his hypophyseal approach Dandy found a pea sized aneurysm arising by a narrow neck from the suprasellar portion of the right internal carotid and resting upon the third nerve. He was able to apply a silver clip on the neck of the aneurysm flush with the wall of the internal carotid. Recovery followed.

It is evident that this procedure when applicable is the optimal one. Study of the reproductions of arteriographs now in the literature suggests that such an opportunity may be relatively frequent in this group of cases.

A new field for surgical treatment of congenital intracranial aneurysms is now in process of development. More detailed study of the symptomatology of these cases before and after rupture may lead to more frequent use of cerebral arteriography as an aid in determining the exact site, the configuration and the size of the lesion. Only upon such a basis can the question of operability, and of the most suitable type of operation be best decided.

[12] DANDY, WALTER E.: Intracranial aneurysm of the internal carotid artery: cured by operation, Ann. Surg., 1938, cvii, 654–659.

REVIEWS

A Primer for Diabetic Patients. By RUSSELL M. WILDER, M.D. 191 pages; 12 × 18 cm. W. B. Saunders Co., Philadelphia. 1937. Price, $1.75.

This familiar diabetic manual, first introduced in 1921, is now its sixth edition. The revision was especially necessary because of the introduction of protamine zinc insulin in the treatment of diabetes. The section dealing with the definition of diabetes should be read by all patients before starting any form of treatment. Sections dealing with the various complications are excellent, particularly the chapter pertaining to the care of the feet. The charts and food tables included in the text are of aid to both patient and physician.

As stated in the preface, "this book is addressed to the patient who is working out a life complicated by diabetes under the guidance of his family physician." This should not discourage the physician from reading the manual, as most valuable information can be obtained in a clear concise manner.

J. S. E.

Hematology. By WILLIAM WAGNER, M.D., D.P.H. 395 pages; 23 × 15 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1938. Price, $4.50.

In writing this book the author has kept in mind the needs of the practising physician as well as those primarily interested in the study of disease by laboratory methods. In general the subject is treated along conventional lines.

The author has devoted special attention to the formation and removal of the blood cells, and the more important theories as to the derivation of the cells are adequately considered. The gross and microscopic anatomy of the hemopoietic tissues in normal and pathological conditions is well covered. The morphology of the cells in stained preparations is well described, but very little attention is given to fresh moist preparations. A chapter of 28 pages is devoted to the technic of the usual simpler laboratory procedures, including sternal aspiration. The technic of supravital staining of leukocytes is not given.

The pathogenesis of the different types of anemia is particularly well discussed, with special emphasis on the part played by the various deficiencies. The anemia following poisoning with benzol and with radioactive substances is also fully discussed. The various diseases of the blood are individually considered, with good descriptions of the clinical symptoms as well as the hematological and pathological features.

The book contains 23 illustrations and 3 colored plates. Although these are for the most part fairly good, they are not up to the standard of the text. The book is up to date and most of the newer work has been included. It is interestingly written, and should be a useful reference book for students and internists.

P. C.

Synopsis of Genito-Urinary Diseases. By AUSTIN I. DODSON, M.D., F.A.C.S. 294 pages; 13 × 20 cm. C. V. Mosby Co., St. Louis. 1937. Price, $3.00.

This is an amazing little book of 294 pages that covers the entire field of this surgical specialty in a surprisingly complete way. It has already gone through two editions. The second edition has been revised to include a discussion of diets influencing infections and calculus formation. Glandular therapy is also introduced and the whole book brought into line with the very newest monographs.

The very simple but very definitive illustrations are ample and clear.

This book contains the essentials that are of value to the internist interested in urology.

W. H. T.

The Fundamentals of Internal Medicine. By WALLACE M. YATER, A.B., M.D., M.S. (in Medicine). 1021 pages; 25 × 17 cm. D. Appleton-Century Company, New York. 1938. Price, $9.00.

In his introduction to this new text, Dr. Yater says that it is designed primarily for the introduction of students to the subject of internal medicine, presenting the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips. Most of the subject matter has been written by Dr. Yater himself, but eleven other authors have also contributed.

The reader is impressed by the book's brevity, clearness, orderliness and lack of confusing overdiscussion. Introductions to the different sections are written so that manifestations of diseases may be correlated with others in the same general groups. Symptomatology and differential diagnosis are stressed by means of diagnostic tables, outlines, and grouping of symptoms that are common to certain classes of disease. Presentations, however, are not from symptomatic, but from etiological and anatomic viewpoints.

The author has followed the English custom of including a chapter on diseases of the skin. There is also a short section on diseases of the ear by F. C. Schreiber, and one on diseases of the eye, by J. A. Greear. These three unusual chapters are intended to correlate knowledge of these specialties with the subject of internal medicine.

Illustrations are used freely, and are uniformly excellent. The publishers should be congratulated on the roentgen-ray reproductions.

"Fundamentals of Internal Medicine" may be fully recommended to medical students. In the reviewer's opinion, it is a valuable addition to our teaching texts.

T. N. C.

The Diary of a Surgeon in the Year 1751–1752. By JOHN KNYVETON; edited by ERNEST GRAY. 319 pages; 21 × 15 cm. D. Appleton-Century Company, New York. 1937. Price, $2.50.

This is a gripping story of surgical training and adventure of a ship's surgeon on the high seas, equally interesting for the laity and for members of the medical profession.

The basis of the story is a period in the life of one John Knyveton whose adventures have been recorded and edited in diary form by Ernest Gray.

The book consists of two parts, the first dealing with the apprenticeship and training of Knyveton in London as a surgeon, which took the lengthy time of six months. An intimate account of the conditions of the time—thrilling tales of grave robbing for suitable cadavers, of the filth of the infirmaries, of numerous amputations with nothing to allay pain, of the appalling hospital death rate. There are occasional periods of diversion with fellow students, walking, conversation at taverns, and trips to the theatre. This Part ends with the student out of funds and successfully qualified for Surgeon's Mate.

The remaining part of the year is spent in His Majesty's service as Surgeon's Mate on the frigate Lancaster. His experiences at this post are exciting. He tells of trouble with scurvy, terrible storms, bloody fights with pirates, and his work on a Spanish isle treating tropical fever. Throughout he is a hard working, honorable and admirable character.

Regardless of the authenticity of the subject matter, this is a thrilling, fast moving, enjoyable book.

H. C. H.

Fearfully and Wonderfully Made. By RENÉE VON EULENBURG-WIENER. 472 pages; 16 × 24 cm. Macmillan Co., New York. 1938. Price, $3.50.

The author, trained primarily in the basic sciences, views the functioning of the human organism, as far as possible, upon an atomic structural basis. The book is constructed about the hypothesis that the obscure and experimentally elusive phenomenon of cellular specificity of function is based upon molecular asymmetry, —the consequent molecular instability affording a readily available source of electrodynamic energy. The attempt is made to apply this explanation to the metabolism of carbohydrates, proteins, and fats, hormones, vitamins, muscle, nervous system, special senses, etc.

The book is written in a readable style and will be most interesting to those who enjoy such speculations.

E. F. C.

COLLEGE NEWS NOTES

New Life Members

Announcement is made of the following additional Life Members of the American College of Physicians, recorded in the order of the receipt of subscriptions:

Dr. O. H. Perry Pepper, Philadelphia, Pa.
Dr. Charles Hartwell Cocke, Asheville, N. C.
Dr. Andrew Henry Hangarter, Brooklyn, N. Y.
Dr. Richard Arminius Kern, Philadelphia, Pa.
Dr. Edward Bridge Bigelow, Worcester, Mass.
Dr. William Simmons Baldwin, Lorain, Ohio
Dr. James Bryan Herrick, Chicago, Ill.
Dr. Lawrence Getz, Ancon, C. Z.
Dr. Clifford P. Rutledge, Shreveport, La.

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Reprints

Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Walter Clarke, F.A.C.P., New York City—2 reprints;
Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Pa.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—January, 1939, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";
Dr. Charles M. Griffith, F.A.C.P., Medical Director of the U. S. Veteran's Administration, sent for the College Library a copy of "A Study of Silicosis" by Dr. Philip B. Matz, F.A.C.P., deceased;
Dr. M. Coleman Harris, F.A.C.P., New York City—1 reprint;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Robert F. Ives, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Harold R. Keeler, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Donald S. King, F.A.C.P., Brookline, Mass.—5 reprints;
Dr. Hubert C. King, F.A.C.P., Lakewood, Ohio—1 reprint;
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—2 reprints;
Dr. Lowell S. Selling, F.A.C.P., Detroit, Mich.—3 reprints;
Dr. G. Louis Weller, Jr., F.A.C.P., Washington, D. C.—7 reprints;
Dr. John H. Willard (Associate), Philadelphia, Pa.—1 reprint;
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint.

Eastern Pennsylvania Sectional Meeting

Under the Governorship of Dr. Edward L. Bortz, F.A.C.P., Philadelphia, the first sectional meeting of Fellows and Associates of the College from Eastern Pennsylvania was held at Philadelphia, on February 3, 1939. Pennsylvania is divided at 78° longitude and the eastern portion is assigned to the Governorship of Dr. Bortz. The program showed a certain amount of novelty and originality, the meeting being referred to as a "Round-Up" and divided into four portions:

1939–40 NOMINATIONS FOR ELECTIVE OFFICERS

In accordance with provisions of the By-Laws, the Committee on Nominations herewith presents the list of nominees for President-Elect and for the First, Second and Third Vice-Presidents for 1939–40. The election of all nominees shall be by the members of the College at its Annual Business Meeting. Nominations may also be made from the floor at the Annual Business Meeting.

Dr. O. H. Perry Pepper, President-Elect, Philadelphia, Pa., will accede to the Presidency.

New Nominations

President-Elect	James D. Bruce, Ann Arbor, Mich.
First Vice-President	Allen A. Jones, Buffalo, N. Y.
Second Vice-President	Gerald B. Webb, Colorado Springs, Colo.
Third Vice-President	J. Morrison Hutcheson, Richmond, Va.

Respectfully submitted,

D. Sclater Lewis,
Henry M. Thomas, Jr.,
Fred W. Wilkerson,
Donald J. Frick,
James Alex. Miller, *Chairman,*
Committee on Nominations

Problems Collegium

1:00 p.m.

1. Rendezvous at the College Home at 4200 Pine Street, Philadelphia.
2. Buffet Luncheon.

Problems Scientific

3:00 p.m.

Medical Laboratories of the University of Pennsylvania

1. Clinic—"Rheumatic Heart Disease," Dr. E. J. G. Beardsley
2. "The Newer Sulphanilamide Compounds," Dr. Sargeant Pepper
3. "Allergy of the Urinary Tract," Dr. Malcolm W. Miller
4. "Pituitary Cachexia," Dr. Charles W. Dunn
5. "Protamine Zinc Insulin," Dr. G. Harlan Wells
6. "The Indications for Collapse Therapy," Dr. William Devitt
7. "Hypometabolism," Dr. Charles L. Brown

Problems Convivial

6:00 p.m.

Penn Athletic Club, Rittenhouse Square

Dinner and entertainment by Dr. Harry Wilmer and his HI-JACKERS OCTETTE (members from the Philadelphia Orpheus Club)

Problems Social

Dr. George Morris Piersol, Toastmaster Secretary-General

Introduction of Distinguished Guests

Dr. O. H. Perry Pepper, President-Elect, American College of Physicians.
Dr. George P. Muller, President-Elect, American College of Surgeons.

Under the able leadership of Governor Bortz's fifteen special committeemen, about one hundred and seventy Fellows and Associates of the College were present, 68 per cent of all the members in this rather large territory. The Buffet Luncheon gave an opportunity for all members to visit the College Headquarters and spend a social hour or two before the formal program began. Due to the large number in attendance it was necessary to schedule the scientific program and clinics in more commodious quarters, and the Medical Laboratories of the University of Pennsylvania, not far removed from the College Headquarters, were utilized.

Among specially invited guests present were:

Dr. Henry M. Thomas, Jr., College Governor for Maryland;
Dr. Lewis B. Flinn, College Governor for Delaware;
Dr. Clarence L. Andrews, College Governor for New Jersey;
Dr. George H. Meeker, Dean of the Graduate School of Medicine, University of Pennsylvania;
Dr. W. A. Pearson, Dean of the Hahnemann Medical College of Philadelphia;
Dr. George P. Muller, President-Elect of the American College of Surgeons.

At the dinner meeting Dr. O. H. Perry Pepper, President-Elect of the American College of Physicians, addressed the group on the work and activities of the College.

Dr. George P. Muller outlined the work and activities of the American College of Surgeons.

This sectional meeting, although the first for the members in Eastern Pennsylvania, was probably the largest and among the most successful of the State sectional meetings of College members in the country.

Inauguration of the Royal Australasian College of Physicians

Dr. Noble Wiley Jones, 3rd Vice President of the American College of Physicians, was appointed the official representative of this body at the inauguration of the Royal Australasian College of Physicians at Sydney, Australia, during December. The following letter was received by Dr. William J. Kerr, President of the American College of Physicians, immediately following the inauguration, from Dr. Allan S. Walker, Hon. Secretary:

> "On behalf of the President and Council of The Royal Australasian College of Physicians, I wish to express our very sincere thanks to your College for giving us the opportunity of having with us as your representative at our Inaugural Meeting Dr. Noble Wiley Jones.
>
> "Dr. Jones has won for himself the regard and friendship of all those he met in our community. His unaffected charm of personality made him a most welcome guest, and his professional erudition gave distinction to our assemblies. He contributed an address on 'Chronic Infection and Atherosclerosis' to one of our scientific sessions which attracted general interest and which we hope to publish in the Medical Journal of Australia.
>
> "Dr. Jones honoured our College by allowing us to confer upon him an Honorary Fellowship. Dr. H. Morley Fletcher, who was the special representative sent from England by the Royal College of Physicians in London, was made our first Honorary Fellow, and it is with pleasure that I inform you that the signature of Dr. Noble Wiley Jones stands as the second on the list of Honorary Fellows in our Register.
>
> "The presence of one of your Vice-Presidents at our Inaugural Meeting was a happy event: it has served to unite our Colleges in the friendship of a common cause, and it will always be a pleasure for us to welcome any of your members to our midst.
>
> "With greetings from our President and Council,
>
> Yours sincerely,
>
> (Signed) Allan S. Walker,
> *Hon. Secretary.*"

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed the Schuylkill County Medical Society, at Pottsville, Pa., on January 10, on "Deficiency Diseases."

Dr. Charles E. Lyght (Associate), Director of the Carleton College Health Service, Northfield, Minnesota, presented the Eighth Annual Report of the Tuberculosis Committee of the American Student Health Association, at the Nineteenth Annual meeting of the Association held in New York City, December 29–30, 1938. The Report summarized the results of a national survey of the work being accomplished in the early diagnosis and treatment of tuberculosis among college and university students. Dr. Lyght is serving his third term as chairman of the Tuberculosis Committee.

Dr. Warren Coleman, F.A.C.P., for a great many years located in New York City, and formerly Professor of Clinical Medicine at the New York University College of Medicine, has accepted the Chair of Professor of Clinical Medicine at the University of Georgia School of Medicine at Augusta, Georgia.

Dr. J. R. Nakada, F.A.C.P., St. Louis, Mo., was the guest of the Jacksonville County Medical Society at Carbondale, Ill., on December 15, 1938, where he presented a paper entitled, "The Medical Management of Duodenal Ulcer."

Dr. Zachary Sagal, F.A.C.P., New York City, was recently advanced to Associate Physician at Bellevue Hospital.

Dr. Priscilla White, F.A.C.P., Boston, Mass., was the guest speaker at the Scientific Meeting of the Allegheny County (Pa.) Medical Society, January 17, 1939, at Pittsburgh, her subject being "Diabetic Children." The entire program was presented by women physicians.

The Thirty-fifth Annual Congress on Medical Education and Licensure was held at the Palmer House, Chicago, February 13 and 14, 1939. At the second session, the Symposium on the Small Hospital, Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, spoke on the "Organization and Management of the Small Hospital" and Dr. William Henry Walsh, F.A.C.P., Chicago, spoke on "Planning for a Small Hospital." Dr. MacEachern is an Associate Director of the American College of Surgeons, and Dr. Walsh is a consultant specialist on hospitals.

Dr. John H. Musser, F.A.C.P., New Orleans, presided at the third session. Among the speakers at this session was Dr. A. J. Carlson, F.A.C.P., Chicago, whose title was "Tenure of Members of the Faculty in Schools of Medicine."

The Federation of State Medical Boards was addressed at its Dinner Meeting by Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, New York, on "Recent Impressions of British Medical Education."

At a subsequent meeting of the Federation Dr. Harold Rypins, F.A.C.P., Secretary, New York State Board of Medical Examiners, Albany, and Dr. Fred E. Clow, F.A.C.P., Secretary, New Hampshire Board of Registration in Medicine, Wolfeboro, delivered addresses on "American Graduates of British Medical Schools" and the "Legal Status of the Intern," respectively.

Dr. Samuel Goldberg, F.A.C.P., Clinical Professor of Pediatrics at Temple University School of Medicine and Senior Attending Pediatrician to the Jewish Hospital, Philadelphia, was recently elected President of the Philadelphia Pediatric Society.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., is President of the Northern Medical Association of Philadelphia (founded in 1846). Dr. A. C. Morgan, F.A.C.P., Dr. J. M. Cahan, F.A.C.P., Dr. William A. Swalm, F.A.C.P., Dr. Mitchell Bernstein, F.A.C.P., and Dr. Nathan Blumberg, F.A.C.P., all of Philadelphia, are among the members of the Executive Committee. At the January meeting of this Association Dr. E. J. G. Beardsley, F.A.C.P., and Dr. Goldstein participated in the Scientific Program. Dr. Foster Kennedy, Professor of Neurology at Cornell Medical School, New York City, addressed the Association on February 20, 1939, on "The Organic Basis of the Mind." The discussion was opened by Dr. A. M. Ornsteen, F.A.C.P., Assistant Professor of Neurology, University of Pennsylvania School of Medicine.

Dr. David Riesman, F.A.C.P., Professor of the History of Medicine, University of Pennsylvania School of Medicine, has been appointed Honorary Chairman of the Centennial Committee of the Association.

OBITUARIES

James Joseph McGuire, 122 West State Street, Trenton, N. J., died at his home October 11, 1938, of arteriosclerosis and nephritis with uremia, at the age of 62.

Dr. McGuire, the son of Felix and Mary Campbell McGuire, was born in Trenton, N. J., May 22, 1876. His father had been engaged in the coal business for many years.

He began his education in the St. John's School in Trenton and entered the St. Joseph College in Philadelphia following that from which he graduated with a B.A. Degree. In 1900, he graduated from the University of Pennsylvania as an M.D.

Following his graduation in medicine, he became an intern in the St. Francis Hospital in Trenton and after one year in that capacity, he began the practice of medicine first on South Broad Street near Center and finally to 122 West State where he was practicing when he died. Together with Dr. G. N. J. Sommer, he led the movement toward this area which is now known as " Medical Row."

In his college days, he was a great baseball player. At Pennsylvania he played in the outfield on the Red and Blue varsity team as well as being a member of the D. J. Wallace baseball club of South Trenton in 1891.

Dr. McGuire was Pediatrician at the St. Francis Hospital, Trenton; consulting Physician, Children's Contagious Diseases Hospital, Trenton; Visiting Physician, Orthopedic Hospital, Trenton, and served for many years on the State Board of Medical Examiners.

He was first appointed to the Board in 1915; served as President from 1921 to 1932 and was Secretary to the Board at the time of his death.

He was a member of the Mercer County Medical Society; the Philadelphia Pediatric Society, Philadelphia Medical Club, the American Medical Association, and a Fellow of the American College of Physicians since 1929.

Aside from his medical interests he was a member of the Knights of Columbus, Catholic Club and the Trenton Country Club. During the World's War, he was a member of the Trenton Draft Board.

Dr. McGuire is survived by his widow, the former Blanche M. Gallagher of Jersey City, N. J.; two daughters, Blanche and Eleanor; a sister, Miss Mary McGuire and two brothers, Timothy and Francis McGuire.

In such a brief span of life he accomplished a great deal. Few knew about his grave illness; it came as a great shock to his friends, and both society and the profession have incurred a great loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey.

DR. FREDERICK J. KALTEYER

Dr. Frederick J. Kalteyer, Clinical Professor of Medicine at Jefferson Medical College, died December 21, 1938, at his home 1707 Spruce Street, Philadelphia, of coronary disease.

Dr. Kalteyer was a Texan by birth. He was graduated from the University of Pennsylvania in 1895 and from Jefferson Medical College in 1899. In 1905 he was elected to the Staff at Jefferson and continued that association up until the time of his death.

Dr. Kalteyer was on the staff of the Philadelphia General Hospital, Consultant-physician to the Delaware County Hospital, and was a member of the University and Merion Cricket Clubs.

In 1923 he was elected an Associate of the American College of Physicians.

From time to time he has contributed to the medical literature.

He is survived by his wife and two sisters.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DR. HENRY WOOLFE BERG

Henry Woolfe Berg, A.B., M.D., F.A.C.P., of 10 East 73 Street, New York City, died December 22, 1938, at the age of eighty.

He was born in Austria on Christmas Day, 1858, and was brought to New York City at the age of three years. He was educated in the public schools of New York City and was an honor student at City College, class of 1878. He entered the College of Physicians and Surgeons of Columbia University, receiving his medical degree in 1881. He then became an assistant to Dr. E. C. Sequin, professor of neurology at Columbia, and was also the attending surgeon at the New York Orthopedic Hospital.

In 1883 he became attending physician at the Willard Parker and Riverside Hospitals and was secretary of their joint board for almost thirty years. During the war he directed the care of soldiers and sailors at the Riverside Hospital during an epidemic of cerebro-spinal meningitis. He was also the author of many papers on serum therapy. His connections with the Willard Parker Hospital covered forty-four years, he being Consulting Physician of this institution at the time of his death. In 1899 he was made adjunct physician at Mt. Sinai Hospital and then associate attending physician. In 1923 he was appointed physician of the isolation service there and retained that post until his death.

Dr. Berg was active in other fields. He gave much time to the study of the Board of Education budget and for twenty years frequently appeared in the interest of taxpayers before the Board of Estimate. He also testified before congressional committees on economic matters and several times received a vote of thanks from the Senate Committees, especially for his

help on immigration laws. In his later years Dr. Berg acquired a collection of rare books in which he took a great interest.

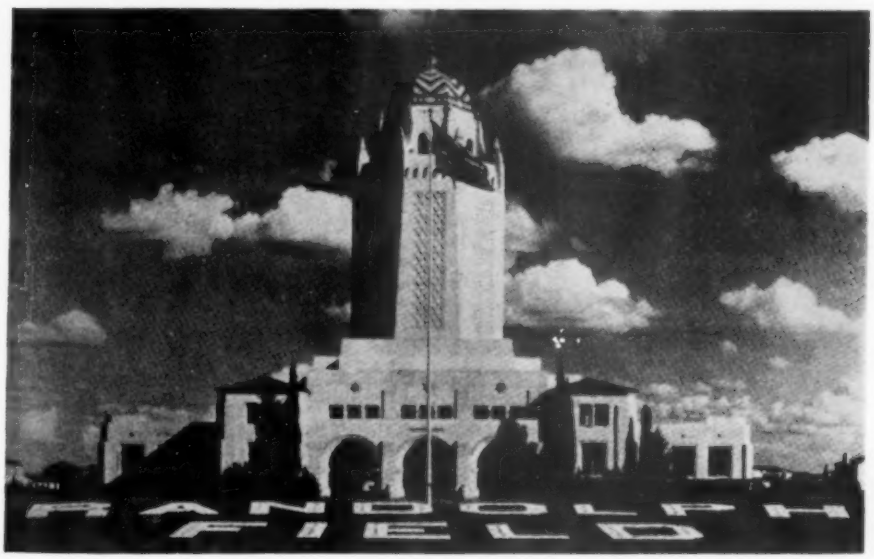
Dr. Berg became a Fellow of the American College of Physicians in 1920 and maintained an uninterrupted and active interest to the end of his life. Although advanced in years he was a regular subscriber to the College journal, the Annals of Internal Medicine.

Dr. Berg was survived by two brothers, Abraham Berg and Dr. Albert A. Berg and by two sisters, Mrs. Samuel D. Levy and Mrs. Delia Warschauer.

C. F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York.

ANOTHER FEATURE FOR THE POST-CONVENTION TOUR TO MEXICO CITY

Lieutenant Colonel Coleridge L. Beaven, M.C., until recently the Commandant of the School of Aviation Medicine at Randolph Field, Texas, one of our Fellows, has invited the members of the Mexico City Post Convention party to visit the School during the stay in San Antonio. Arrangements are now being worked out to make this possible, and it will be one of the high-lights of our short stop in San Antonio. Lieutenant Colonel Fabian L. Pratt, who has succeeded Lieutenant Colonel Beaven as Commandant of the School of Aviation Medicine, and Lieutenant Colonel N. C. Mashburn, the Assistant Commandant, will receive the party on its arrival at San Antonio.



Air Corps Training Center Headquarters, Randolph Field, Texas.

The School of Aviation Medicine had its origin during the World War as the Medical Research Laboratory located at Hazelhurst Field, Mineola, Long Island, N. Y. In 1919 the School for Flight Surgeons was added and the first class graduated. That same year the school was moved to Mitchel Field and in 1922 the name was changed to The School of Aviation Medicine. In 1931 the school was moved to its present location at the Air Corps Training Centre which affords a splendid opportunity for the teaching of aviation medicine from a practical standpoint.

To the excellent clinical facilities offered for teaching by Army, State and City hospitals adjacent to Randolph Field, there are the three classes of flying trainees entering the Training Center annually, numbering around

1,000. These highly selected young men, ranging in age from 21 to 27, are in the pink of physical condition to begin with and are kept so by living in an ideal as well as controlled hygienic environment. This group serves as excellent material for clinical work as well as for the investigation and solution of the many problems connected with aviation medicine.

In addition to the privilege of using these trainees for working out various laboratory experiments, the medical students have the opportunity to observe their progress on the flying line and to see first hand just what type does well in flying training and what type does not. They study the "daily flying log books" and learn from the comments of the flying instructors just why it is impossible to teach certain types of individuals to fly military airplanes.

Since learning to fly is complicated and flight surgeons are expected to select young men who will do well in the job of learning to fly, it becomes necessary for him to know as much about flying as possible. This can be accomplished best by having the Flight Surgeon work at the job of learning to fly. All students at the School of Aviation Medicine are given ten hours flying training. In this training the medical student goes through the same routine as flying students and gains first hand information about the problems of learning to fly.

There are other features on which we are now working that will prove very delightful and which will be announced later.